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The University of Dublin, Trinity College

Ollscoil Átha Cliath, Coláiste na Tríonóide

The Effects of Depression and Electroconvulsive Therapy on Retrospective Memory and General Cognition: a longitudinal study.
PhD Thesis

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May 2012

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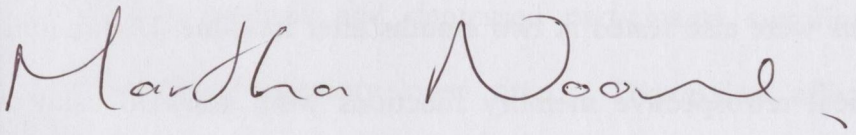
Declaration

This work has not been submitted as an exercise for a degree at this or any other University. Two main studies make up this thesis. In the first study reported, the Mem-Dep Study, I designed the study with help from my supervisor and carried out the majority of the assessments. I carried out 72% of the assessments and three students in my department carried out 28% of the assessments.

In the second study, the EFFECT-Dep Trial, I worked as part of team totalling nine different researchers over a period of three and a half years. As one of the nine researchers working on the EFFECT-Dep Trial I completed 24% of all assessments carried out.



Martha Noone

Summary

The objectives of this work were to investigate the effects of depression on retrospective memory, in addition to attention, psychomotor and executive function, in depressed patients receiving pharmacotherapy treatment compared to healthy controls (The Mem-Dep Study). The second objective was to examine retrograde memory function in patients in a randomised controlled non-inferiority trial investigating the effectiveness and side-effects of high-dose Right Unilateral (RUL) ECT and standard Bitemporal (BT) ECT in severe depression (EFFECT-Dep Trial).

Cognitive test batteries were administered to severely depressed in-patients and controls participating in both studies at baseline and throughout 6-12 months follow-ups. Depressed participants were also tested at two months after baseline. Both public events and autobiographical retrospective memory functions were assessed using a specially constructed Public Events Questionnaire and the Columbia Autobiographical Memory Interview Short-Form (AMI-SF) respectively. In the first section of the Mem-Dep Study depressed and control participants were compared at baseline and changes at two months follow-up were also assessed within the depressed group. The second part of the Mem-Dep Study assessed change in performance over time at six and 12 month follow-up in depressed participants and controls. Participants in the ECT groups were randomised after baseline assessment and compared at End of Treatment, 3 months and six months post-treatment. Severity of depression was assessed using the Hamilton 24-item rating scale for depression (HDRS 24).

Findings in The Mem-Dep Study indicate that at baseline the depressed group scored significantly lower than controls on measures of autobiographical memory and psychomotor speed. At two month follow-up the depressed group had significantly

improved on clinical measures but showed a significant decrease in performance of autobiographical memory. A sub-group of the baseline sample was also assessed at six and 12 month follow-up. In this sample there were no significant differences between groups on any measure although the difference on autobiographical memory at 12 months approached significance. Baseline autobiographical memory scores only approached significance in this sample, in contrast to the significant difference found in the larger baseline sample. Both groups had a significant loss of consistency in autobiographical recall between baseline and six month follow-up. In the EFFECT-Dep Trial the BT ECT group performed significantly worse at end of treatment on the Public Events Questionnaire, whereas the RUL ECT group did not, however differences in the BT ECT group did not persist at three and six month follow-up.

Both controls and depressed participants significantly lose consistency in autobiographical memory over time. Depression affects retrospective memory functions differentially, with autobiographical memory being impaired while public events memory is not affected. Preliminary results of the EFFECT-Dep Trial indicate that BT ECT may have a greater effect upon retrograde memory than RUL ECT. However, the effects of ECT on public events memory are transient.

Acknowledgements

While working on this research study I completed most of the recruitment and assessment in The MEM-Dep Study, and worked as part of the research team on the EFFECT-Dep study. I am extremely grateful to my colleagues on the EFFECT-Dep team including Ana Jelovac, Diarmaid O'Lonorgain, Sinead Lambe and Sarah Roeder for their help and assistance over the last few years.

In particular I would like to acknowledge the help and assistance of Dr Maria Semkovska with the planning and statistical analyses for the reliability and validity study on the Public Events Questionnaire, as well as for training in neuropsychological assessment and numerous pieces of advice in terms of research and psychology over the course of this research.

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I am most grateful to my parents, sisters and friends for unwavering encouragement, belief, and support over the last few years. I am indebted to Lizzie, Aaron and Brian for coming to my rescue at the final hurdle!

This journey has been shared from the beginning, through all its twists, turns, highs and lows, with Brian, whose empathy and love and linguistic prowess have been invaluable.

Finally, I would not have been able to complete this research without the help of all the participants who gave their time so graciously, and who inspired me in so many ways.

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ABBREVIATIONS

ABM: Autobiographical memory

ACE: Addenbrooke's Cognitive Examination

ACE-R: Addenbrooke's Cognitive Examination, Revised edition

AMI: Autobiographical Memory Inventory

AMI-SF: Autobiographical Memory Inventory Short-Form

ANOVA: Analysis of variance

ATHF: Antidepressant Treatment History Form

BDI: Beck Depression Inventory

BDI-II: Beck Depression Inventory, version two

BDNF: Brain derived neurotrophic factor

BT ECT: Bitemporal Electroconvulsive Therapy

BPRS: Brief Psychotic Rating Scale

BSRT: Buschke Selective Reminding Test

CAPIT-HD: Core Assessment Program for Intracerebral Transplantation in Huntington's Disease

Df: degrees of freedom

DLPFC: Dorsal-lateral prefrontal cortex

DSM-III/IV: Diagnostic and Statistical Manual for Mental Disorders, version three/four

ECT: Electroconvulsive Therapy

EM: Estimation maximisation

EOT: End of Treatment

EQ1: Events Questionnaire time-period 1

EQ5: Events Questionnaire time-period 5

EQ10: Events Questionnaire time-period 10

EQ15: Events Questionnaire time-period 15

F: F statistic in ANOVA

FCSR: Free and Cued Selective Reminding

HDRS: Hamilton Depression Rating Scale

ICC: Intraclass Correlation Co-efficient

IQ: Intelligence Quotient

LOPFC: Lateral-orbital prefrontal cortex

LTM: Long-term memory

MAR: Missing at random

MAOI: Monoamine oxidase inhibitors

MCAR: Missing completely at random

MCG: Medical College of Georgia

MDD: Major Depressive Disorder

MMSE: Mini Mental State Examination

N: number

NART: National Adult Reading Test

NaSSa: Noradrenaline and Specific Serotonin antidepressants

PANSS: Positive and Negative Syndrome Scale

PEQ: Public Events Questionnaire

RCT: Randomised controlled Trial

ROCF: Rey-Osterrieth Complex Figure

RUL ECT: Right Unilateral Electroconvulsive Therapy

SCID-I: Structured Clinical Interview for the DSM-IV, Axis 1

SIGH-D: Structured Interview Guide for the Hamilton Depression Rating Scale

SNRI: Serotonin noradrenaline re-uptake inhibitor

SPSS: Statistical Package for the Social Sciences

SSRI: Selective serotonin re-uptake inhibitor

ST: Seizure Threshold

STM: Short-term memory

T: t-statistic

TCA: Tricyclic antidepressant

TMT: Trail Making Test

UL ECT: Unilateral Electroconvulsive Therapy

VEGF: vascular endothelial growth factor

VMPFC: Ventromedial prefrontal cortex

WAIS-R: Wechsler Adult Intelligence Scale, Revised

Z: z-statistic

CHAPTER 1 INTRODUCTION

1.1 Depression

1.1.1 Prevalence

Depression can be characterised by low mood and loss of interest and enjoyment in everyday things, as well as a range of emotional, physical, behavioural and cognitive changes (National Institute for Clinical Excellence, 2009). Depression is a common and widespread illness, with lifetime prevalence rates estimated to be as high as 10-25% for women and 5-12% for men (American Psychiatric Association, 2000). It is predicted to become the second leading cause of disease burden in the world by the year 2020 (Mathers and Loncar, 2006). The average age of onset of a first episode of depression is in the mid-twenties and the disorder is highly recurrent, seemingly linked to an earlier age of onset and number of previous episodes experienced (Burcusa and Iacono, 2007). Approximately two thirds of people will remit after varying levels of treatment, however one third may continue to experience symptoms, without full remission (Rush et al., 2006).

1.1.2 Aetiology

There are many factors that can contribute to the development of a depressive episode, including stressful life events, environmental factors like childhood neglect and genetic vulnerability, and perhaps in particular the interplay between genes and environment (Goldberg, 2006). In the case of genetic contributing factors, depression has been estimated to have a 40-50% heritability component, based on twin and family studies (Levinson, 2006).

1.1.3 Diagnosis

Over the years criteria have been developed and refined for accurate diagnosis of depression. Most often depression is diagnosed according to Diagnostic and Statistical Manual of Mental Disorders (DSM), the current version of which is the DSM-IV, text-revised edition (DSM-IV-TR) (American Psychiatric Association, 2000), or the International Classification of Diseases (ICD) criteria, from the ICD-10 (2007 revised edition) (World Health Organisation, 2007). These criteria allow for precise distinction from everyday changes in mood, as well as from other disorders such as anxiety or dementia. The DSM-IV-TR (American Psychiatric Association, 2000) lists criteria for an initial depressive episode as a minimum of two weeks of low mood, or lack of interest in almost all activities, where no pleasure is gained from any usual activities. In addition to this, the person must also report at least four other symptoms of depression, such as: changes in appetite, weight, sleep patterns or psychomotor activity; decreased energy; difficulty in thinking, concentrating or making decisions; recurrent thoughts of death or suicidal thoughts or behaviours; feelings of worthlessness, or excessive guilt (American Psychiatric Association, 2000). Symptoms must be present most of the day nearly every day for at least two weeks and must represent newly experienced symptoms or worsened symptoms when compared with usual functioning. Depression can be described as a heterogeneous disorder in which core symptoms and additional symptoms vary greatly between cases (Rush, 2007).

Occurrence of one or more depressive episodes without history of manic, mixed or hypomanic episodes, that are not due to a medical condition, substance abuse, or schizoaffective, schizotypal or schizophreniform disorder is referred to as major depressive disorder. Major depressive disorder (MDD) can be classified according to its severity as mild, moderate or severe.

1.1.4 Types of depression

Depression consists of two main types, with various subtypes. The two main types are unipolar depression and bipolar depression. Unipolar depression consists solely of depressive phenomena, whereas bipolar disorder involves depressed mood and at least one manic, hypomanic or mixed state episode (Sadock and Sadock, 2000). A manic state can be described as a discrete period in which an abnormal and persistently elevated, or irritable, mood prevails (American Psychiatric Association, 2000). Hypomania also involves elevated and/or irritable mood, but the observable change in functioning should not be severe enough to cause marked impairment of social or occupational functioning, or to require hospitalisation (American Psychiatric Association, 2000). Sub-threshold diagnoses of dysthymia and cyclothymia are also common. Dysthymia is often viewed as a low-grade, chronic form of MDD (Brunello et al., 1999). The symptoms of dysthymia must have been present for at least two years upon diagnosis, during which periods of relief from depressive symptoms lasted no longer than two months (American Psychiatric Association, 2000). Cyclothymia is similar in that it is a low grade chronic disorder containing numerous periods of brief and mild depressive and hypomanic states (Howland and Thase, 1993).

1.1.5 Functional Neuroanatomy and Neurobiology

Studies investigating the underlying changes to functional neuroanatomy in people with MDD have found abnormalities in prefrontal and limbic structures and their interconnected circuitry. Areas of the prefrontal cortex implicated include: the ventromedial prefrontal cortex (VMPFC), which is involved in emotional processes, including pain, aggression, sexual function and eating behaviours; the lateral orbital prefrontal cortex (LOPFC), involved in risk assessment and modulation of perseverative and maladaptive behaviours; and the dorsolateral prefrontal cortex (DLPFC), which

involves cognitive and executive functions, sustained attention and working memory processes (Maletic et al., 2007, Koenigs and Grafman, 2009). It is suggested that the VMPFC and LOPFC are hyperactive in MDD, which may affect associated functions such as pain, aggression and perseverative behaviour, as mentioned above, whereas the DLPFC may be underactive, thus resulting in impaired maintenance of executive and attentional functions (Maletic et al., 2007, Koenigs and Grafman, 2009). The anterior cingulate cortex, ventral striatum, amygdala and hippocampus are also involved in MDD. The ventral striatum is involved in targeting reward and motivational processes while the amygdala is involved in emotion, threat detection and fear conditioning. The hippocampus has been found to have a reduced volume in studies of depressed participants compared to healthy controls (Videbech and Ravnkilde, 2004) which has been shown to be related to the number and duration of previous episodes of depression (Sheline et al., 2003, Colla et al., 2007).

In addition to studying the anatomical areas of the brain thought to be involved in depression, chemical and molecular changes to brain functioning have been examined. The most prominent theory in this respect has been the monoamine hypothesis of depression. The monoamine hypothesis postulates that depression arises from deficient neurotransmission of monoamines such as noradrenaline (Schildkraut, 1965) and serotonin (Lapin and Oxenkrug, 1969). Recent research has focused on the role of neurotrophic factors in depression. Chronic antidepressant treatment causes up-regulation of aspects of neurogenesis, including increased proliferation and survival of neuronal cells, in a time-line consistent with the appearance of beneficial effects of antidepressant treatment (Warner-Schmidt and Duman, 2006). Neurotrophic factors such as brain derived neurotrophic factor (BDNF) and vascular endothelial growth

factor (VEGF) have been associated with this process (Warner-Schmidt and Duman, 2006).

1.2 Cognition and Depression

Given the adverse effects of MDD on neurobiological functioning, it is not surprising that cognitive impairments have been consistently reported as symptoms of depression. In addition, symptoms such as difficulties concentrating and complaints of poor memory are so common in MDD that they are listed as one of the criteria that may be met in diagnosing the disorder: "Diminished ability to think or concentrate" (American Psychiatric Association, 2000). As a result, studies of neuropsychological functioning in depression are becoming more and more common. Such studies have found that patients can exhibit a range of cognitive impairments, including disruptions to memory, attention, psychomotor activity and executive function during a depressive episode (Austin et al., 2001). However, it is not clear whether these impairments are due to the depressed state, in which mood affects cognition, or to some endogenous trait in individuals who suffer from depressive disorder. One method of studying the issue of whether cognitive impairments in depression are state or trait related is to examine patients both during a depressive episode and when the episode has remitted. This allows us to examine whether cognitive functioning varies with mood or whether the impairment is a stable trait, independent of emotional state. However there is also the possibility that impairments found during remission may not reflect a trait marker, but instead may be an indication of persistent neurotoxic effects of the depressive episode on the brain. Thus the cognitive changes referred to above (Austin et al., 2001) as well as neurochemical changes shown post-depressive episode (Bhagwagar and Cowen, 2008) may have been caused by the depressive episode itself, rather than having been

there to begin with. In addition, it may also be possible that socio-adaptive recovery of functions in depression, that is return to pre-morbid social and cognitive function, may in fact take longer than it takes for the symptoms of the depressive episode to remit (Greer et al., 2010).

The focus here will be on those functions found to be affected in depression, beginning with a review of findings pertaining to attention, psychomotor speed and executive function, followed by a separate discussion of memory function, both in the acute phase of depression and over long-term follow-up.

1.2.1 Types of Cognition

Attention refers to the general ability to become aware and receptive of stimuli in the surrounding environment (Parasuraman, 1998). Attention can be divided into four separate functional parts that include focused/selective attention, sustained attention/vigilance, divided attention and controlled/alternating attention (Gitelman, 2003, Lezak, 2004). Focused or selective attention refers to the ability to attend to one or two target items while suppressing the awareness of any other stimuli. Sustained attention refers to the ability to focus and maintain attention on one thing over a period of time, or to detection of an unexpected or unusual event. Divided attention is the ability to attend to more than one task, or different elements within a task, at one time. Alternating attention, or controlled attention, is the ability to stop attending to one stimulus in order to attend to another (Gitelman, 2003). It has been suggested that some deficits of attention may be due to slowed processing rather than attentional deficit (Lezak, 2004).

Another cognitive function that is frequently reported as being impaired in depression is psychomotor speed. The term psychomotor can be used to describe

behaviour involved in both mental and motor processes and is involved in gait, speech, facial expression, gestures, fine motor behaviour and thinking (Pier et al., 2004). Executive functions are those involved in more complex mental operations and involve behaviours such as problem solving, self-monitoring, behaviour modification and coordination, planning and organisation, and goal orientation (Elliott, 2003).

1.2.2 Cognition in Depression

Miller attempted the first review of research on the cognitive aspects of depression ranging from the few studies of the 1920's and 1930's up to the more frequent research of the 1960's and 1970's (Miller, 1975). The Miller study concluded that depressed participants exhibit deficits in a range of cognitive, motor and perceptual tasks. However, many early studies did not differentiate between depressive subtypes and frequently examined the impairment in MDD relative to other psychiatric disorders such as schizophrenia. Although subsequent research improved by focusing on impairments in depression compared to healthy controls, problems such as lack of definition around the depressive diagnosis persisted and systematic research in this area remained sparse until the 1990's (Veiel, 1997). However, studies in the area have become more frequent and recent reviews of the literature have reported consistent findings of deficits in attention, executive functions, psychomotor speed and processing speed during the acute phase of a depressive episode (Gualtieri et al., 2006, McDermott, 2009, Zakzanis et al., 1998) . In addition to studying the acute cognitive effects of MDD, researchers have begun to focus more on possible long-term impairments arising from MDD. Evidence of persisting deficits, in the absence of depressed mood, would suggest that cognitive impairment is a trait feature of those who suffer from depression, rather than owing simply to the mood state. Related neurobiological studies have

recently suggested that changes to the brain arising from a depressive episode, such as reduced hippocampal volume and abnormalities in neurotransmission, may persist after the clinical symptoms of depression have remitted (Quinn et al., 1996, Hansen et al., 2012)

1.2.2.1 Attention

Findings regarding the effect of depression on attention have differed across studies. This is due in part to lack of consistent definition of attention within studies and also to how it is measured across studies. In the current discussion, digit span forward from the Wechsler Adult Intelligence Scale-Revised (WAIS-R); (Wechsler, 1981), digit symbol, Stroop Interference test and letter cancellation will be included under measures of attention (in line with Lezak et al, 2004). In one meta-analysis, in which strict inclusion criteria were applied (requiring all studies to have well matched controls and depressed groups), attention was not found to be impaired in currently depressed patients, relative to controls, on measures of simple attention as measured by digit span forward (Veiel, 1997). Similarly, another meta-analysis found that depression had no effect on digit span forward performance, however in this case digit span was used to assess primary memory, not attention (Zakzanis et al., 1998). The same meta-analysis however, did find attention to be adversely affected by depression using tests based on different attentional functions: letter cancellation, WAIS-R arithmetic sub-section (freedom from distractibility), Stroop interference (attention/concentration) and WAIS-R Digit symbol task (sustained attention) (Zakzanis et al., 1998). In the same way, a different study found that the depressed group performed significantly worse than controls on a measure of sustained attention (Sustained Attention Response Task, (Robertson et al., 1997, Farrin et al., 2003)). Despite the inconsistencies in reporting of

attentional deficits, it seems clear that there is some form of impairment in attentional function during a depressive episode, especially in tests of sustained or selective attention, and where effortful attention is required (Gualtieri et al., 2006). More recently, general impaired cognition in depression has been described as being due to deficits in attentional control (Gotlib and Joorman, 2010), which may be related to executive functioning.

With regard to persisting attentional deficits, findings are also mixed. Biringer and colleagues found that at two year follow-up a recovered depressed group (n=30) had improved performance on tasks of attention relative to baseline, but did not perform to the baseline level of healthy controls (n=50) (Biringer et al., 2007). Recent evidence suggests that at follow-up of less than six months a relatively stable impairment in attention persists (Douglas, 2009). Similarly, other studies have found a persistent impairment in attention in patients who were fully remitted for at least three months, compared to healthy controls (Weiland-Fiedler et al., 2004, Paelecke-Habermann et al., 2005). However, tasks of simple attention were not used in these studies, instead these findings relate to various measures of complex and effortful attention.

1.2.2.2 Psychomotor Processing

Psychomotor speed and processing speed have been shown to be affected during a depressive episode (Parker et al., 1993) and psychomotor retardation is a common symptom of MDD (American Psychiatric Association, 2000). Simple reaction time has been suggested to measure cognitive slowing in depression (Caligiuri and Ellwanger, 2000) and has been found to be impaired in a study that examined untreated MDD patients (n=75) compared to healthy controls (n=83 (Kertzmana et al., 2010)). Similar results were also found in a smaller study of depressed (n=38) and control (n=38)

participants (Pier et al., 2004). Most recently, one study has demonstrated an impairment of psychomotor speed in a depressed group (n=68) compared to a well matched group of healthy controls at baseline (n=50) (Douglas et al., 2011). However, the latter study included both bipolar depressed participants as well as those with co-morbid panic disorder with agoraphobia, post-traumatic stress disorder and alcohol misuse; therefore these results cannot be limited to depressed groups.

Regarding persisting impairments in psychomotor processing, responders to treatment for depression have been found to perform at an equal level to controls, despite being impaired at baseline (Douglas et al., 2011). Another study found no significant differences between remitted (n=11) and non-remitted (n=14) participants at a follow-up (two to six months post baseline), indicating that impairment may be due to trait not mood-state deficits (Gallagher et al., 2007). Despite this finding it was also noted that non-remitted participants performed worse than matched healthy controls at follow-up, whereas remitted participants did not.

1.2.2.3 Executive Function

In recent years studies have provided reasonably consistent findings of impaired executive functioning during a depressive episode (Austin et al., 2001). Depressed participants have been shown to be impaired on measures of verbal fluency, inhibition, set-maintenance and set shifting compared to healthy controls (Stordal et al., 2004, Douglas et al., 2011). In addition, functions such as cognitive flexibility, inhibition and planning have been shown to become more impaired as severity of depression increases (McDermott, 2009). Semantic fluency has been reported to be more affected by depression than phonemic fluency in previous meta-analyses (Veiel, 1997, Zakzanis et al., 1998), however when study differences are accounted for, by examining only

studies in which both phonemic and semantic fluency were assessed, it appears that there is no difference between performance on the two tasks (Henry and Crawford, 2005).

As demonstrated in other cognitive domains, the evidence for persisting executive deficits in depression is mixed. In some cases executive functioning has been found to improve significantly in patients who responded to treatment (Jaeger et al., 2006, Beblo et al., 1999), however participants in these studies were not compared to healthy controls. Other studies have shown that executive functions remain impaired compared to controls after the depressive episode has remitted, however these studies only tested participants when remitted and so change from baseline was not accounted for (Paradiso et al., 1997, Paelecke-Habermann et al., 2005). It may be the case that while some aspects of executive function improve upon remission of depression, others do not. In one study (n=19) verbal fluency was found to improve at discharge with a decrease in depression severity, while performance on the STROOP interference task remained impaired (Trichard et al., 1995).

1.3 Memory

The nature of memory has fascinated philosophers and psychologists alike for hundreds of years and, although Aristotle was considering the nature, cause and location of memory and reminiscence in 350 BC, it is generally Ebbinghaus (Ebbinghaus, 1885) who is recognized as the first person to systematically and experimentally study human memory. Since the 1950's the study of human memory has expanded rapidly and between the laboratory driven theories of experimental cognitive psychology and more clinically motivated neuropsychology research there currently exists a plethora of

research findings and theories pertaining to the workings of memory. However, despite the enormous amount of research that has been carried out, there still remain many controversies and conflicting opinions as to how and where memory is encoded, stored and retrieved.

1.3.1 Divisions of memory

1.3.1.1 Short-term Memory

Until the 1960's the prevailing view was that human memory was a unitary system, the same one system being responsible for all functions involved in the "indivisible complex entity" that was memory (Tulving, 1999). However findings from patients with dissociable impairments in different aspects of memory function (where some aspects of memory were spared and others affected with the reverse pattern found under different conditions) led researchers to question whether memory might consist of different systems, with distinct functions, rather than one unitary system (Scoville and Milner, 1957, Milner, 1966). These clinical findings led to new avenues of research that focused on memory systems with more than one component. The Atkinson and Shiffrin (1968) model included both a short-term component and a long-term component to memory. Information was thought to pass from the environment to short-term memory (STM) through "sensory registers" (Atkinson and Shiffrin, 1968). The longer information was held in the short-term store the higher the chances of it being transferred into long-term memory (LTM) (Baddeley, 2002). However, evidence from patients with neuropsychological impairment again challenged some assumptions of this theory, in particular that learning depended on the amount of time an item was held in STM and that it was necessary for information to pass through STM before it could be kept in LTM (Craik and Lockhart, 1972).

Newer theories proposed that STM itself was not unitary and suggested a three system model of working memory instead (Baddeley and Hitch, 1974). The working memory model comprises the following: a phonological loop, a short-term memory store that involves a sub-vocal rehearsal process; the visuospatial sketch-pad, for short-term storage of visual and spatial information; and the central executive, an attentional control system. A fourth component, the episodic buffer, was added more recently (Baddeley, 2000) as a temporary store for multimodal information. This episodic buffer integrates information from the systems within working memory and long-term memory (Baddeley, 2002). Thus, working memory is a system for manipulation of information, rather than simply a holding place for it before it transfers to long-term memory (Nadel and Hardt, 2011). This working memory model also displays the separate processing of verbal and visual material, an important dissociation in memory research.

1.3.1.2 Long-term Memory

LTM refers to memories that can last for days, months or years (Nadel and Hardt, 2011) and has long been studied in relation to its form and functioning in both healthy controls and memory-impaired individuals. Long-term memory has also been suggested to be made up of multiple components. The most commonly accepted version of this "fractionation" of memory (Squire and Zola-Morgan, 1991) is presented in Figure 1.

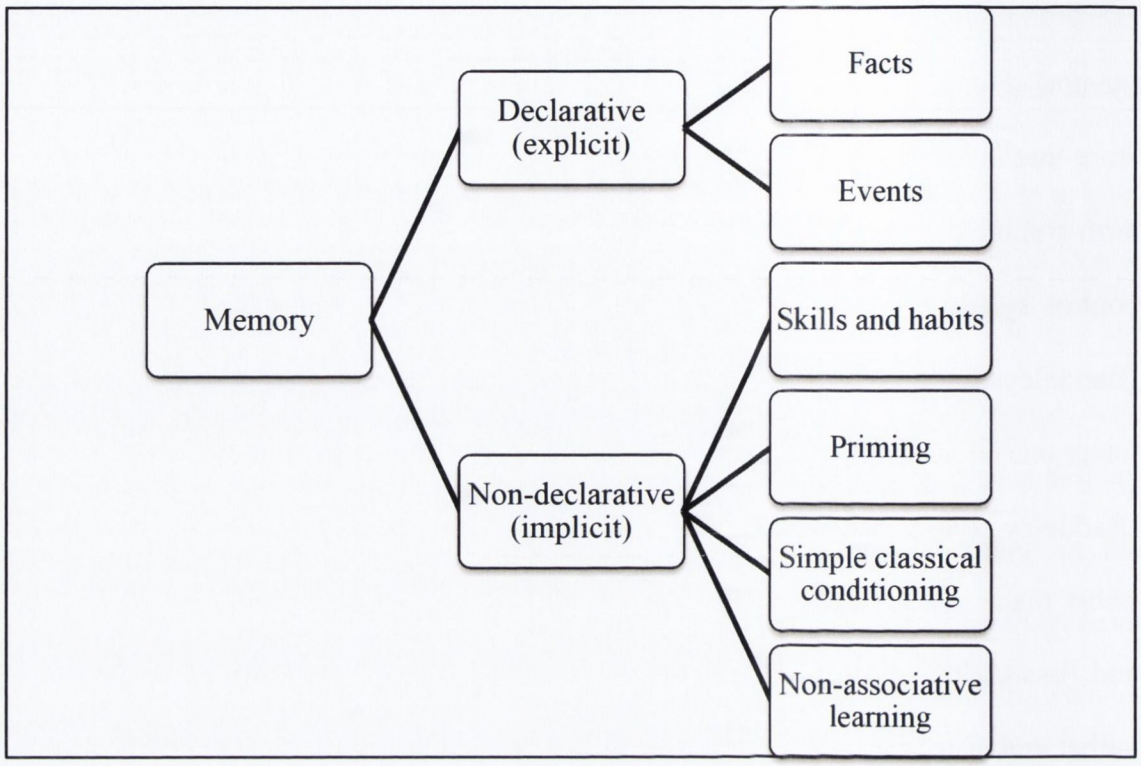


Figure 1 Divisions of long-term memory (Adapted from (Squire and Zola-Morgan, 1991)

LTM is generally divided into two types: declarative and non-declarative memory, referring to memories that can be consciously and unconsciously recalled, respectively (Squire and Zola, 1996). Non-declarative memory refers to skills and habits, priming, classical conditioning and non-associative learning (Baddeley, 2002). Declarative memories can be sub-divided into episodic and semantic memories (Tulving, 1983) and are the main focus of the current research.

Episodic memory refers to memories that have a temporal and spatial association, while semantic memory refers to memories for facts that are recalled without specific time or place context, for example the letters of the alphabet or general knowledge of the world (Baddeley, 2002). Long-term memory can refer to any memories acquired from a few minutes to a few decades ago (Evans, 2004), which in turn can be described as "recent" or "remote" long-term memories. There is difference of opinion as to how to define the cut-off for each type of memory. Some researchers describe remote memory as anything from days ago to decades ago (Moscovitch et al., 2006) while others view it as a more clinical term where recent memory is anything stored in the last few hours, days or months and remote refers to older childhood memories (Strub and Black, 2000). Perhaps more useful in research terms is the view that recent memories may cover anything up to three years ago, and remote memories refer to anything older than that (Squire et al., 1981).

Loss of memory is generally referred to as amnesia. Amnesia can be divided into two types. Retrograde amnesia refers to loss of previously learned information from before a fixed point, or particular occurrence, for example before a head injury or an operation. Anterograde memory refers to an inability to recall information learned after a fixed point. In some cases a fixed point, or occurrence of a particular event, cannot be determined for the onset of retrograde or anterograde amnesia. This may occur for

example when memory impairments are reported during a depressive episode, but the beginning of the episode cannot be clearly defined. In this case the inability to recall previously learned information is referred to as an impairment of retrospective memory function, instead of retrograde amnesia (Lezak et al., 2004).

The distinction between verbal and visual information seen in working memory also continues into the study of LTM. Verbal working memory and long-term memory are often assessed using word lists such as the Buschke, Rey Auditory Verbal Learning Test and California Verbal Learning Test. These tests may ask for recall/recognition of presented information immediately, thus assessing working memory, or after a delay, thus assessing anterograde memory.

1.3.1.3 Retrospective Memory

A further dichotomy in LTM is that of autobiographical memory and public events memory. Autobiographical memory refers to memory of personal events in one's life whereas public events memory examines events in the public domain such as politics, business, entertainment, crime, disasters, sports, science, national and international news events (Meeter et al., 2010). Questionnaires pertaining to both memory types were originally used as general measures of long-term memory (Stieper et al., 1951, Warrington and Silberstein, 1970). However, as their use increased studies began to examine possible dissociations between impairment of autobiographical memory and public events memory. Yasuda and colleagues (1997) describe a patient with left temporal lobe necrosis who was severely impaired on measures of public events and famous faces memory tests, but unaffected on measures of autobiographical memory (Yasuda et al., 1997). Another study has found similar results in a patient with right temporal lobe degeneration (Kitchener and Hodges, 1999). In contrast to these

findings, some researchers have found impairments in autobiographical memory with little effect on public events memory (O'Connor et al., 1992).

The distinction between autobiographical memory and public events memory has often followed the conceptual division of episodic and semantic memory respectively (Kapur, 1999). However, recent studies have shown that these conceptual divisions of function are far more complex than originally thought and, rather than following strict dichotomies, memory for public events and personal information is often associated (Brown, 1990). In studies of healthy controls, researchers have shown that autobiographical memory and public events memory individually contain elements of both episodic and semantic memory (Piolino et al., 2002, Piolino et al., 2007). In the case of public events memory it was found that this memory type comprised factual knowledge that was associated with semantic function (e.g. name/nationality/occupation of a famous person) and event knowledge that was associated with episodic memory (e.g. an event the person is famous for and where, when or how it happened (Piolino et al., 2007)). Similarly, autobiographical memory was found to be composed of both autobiographical semantic (e.g. the name of my school, my teacher, etc.) and autobiographical episodic subcomponents (events that happened in school, etc. (Piolino et al., 2002)). The ambiguity between definitions in this area has been related to researchers using two different concepts of episodic memory: one which relates to the acquisition of declarative information on one occasion and its successful retrieval on a subsequent occasion; and a second which refers to episodic memory as providing conscious recollection of personal events from the subject's personal past (Wheeler et al., 1997).

However, initial measures of public events and autobiographical memory were less concerned with theoretical dichotomies, and were considered as a way of studying

general remote memories. Public events questionnaires allowed for assessment of memories whose details could be independently verified as actually having occurred (Warrington and Silberstein, 1970), and were based on common experience across participants (Warrington and Sanders, 1971). This was in contrast to measures of autobiographical memory which were inherently subjective and varied in accordance with participants' individual personal experiences. Developments and current opinions regarding measurement of retrospective memory differ depending on the nature of the research being conducted and so warrant further discussion here.

1.3.1.3.1 Measuring Public Events Memory

Public Events questionnaires (Howes and Katz, 1988, Warrington and Silberstein, 1970, Squire et al., 1989, Reed and Squire, 1998, Meeter et al., 2010) contain questions about memorable events that have occurred over a number of years, from recent to remote time-periods. They are often presented firstly in a free recall format, followed by a recognition format where participants are provided with the correct answer along with two or three incorrect answers and asked to choose the correct answer from the group. Questions on public events tests are often grouped into a number of time-periods in order to assess the age of the memory and participants are also often grouped by age in order to facilitate comparisons of chronological age.

Public Events questionnaires have been studied with regard to participant demographics such as age, gender and media interest. Both the age of the memory being examined and the influence of chronological age on forgetting have been studied with public events questionnaires. Studies have generally shown that older participants do not perform as well as younger ones on measures of memory for events that all have lived through (Squire, 1975, Howes and Katz, 1988, Bizzozero et al., 2004). In addition,

younger participants who were aged less than 12 years old performed significantly worse than those who had been older than 12 at the time of the event (Howes and Katz, 1988). Some authors have noted that while recent memory performance decreased with age, recall of remote memories remained at a constant level across time-periods (Howes and Katz, 1988, Squire, 1975). However, others have shown more remote memories to be more susceptible to forgetting (Warrington and Sanders, 1971). Gender analyses have shown better performance for males on political items, sports, business and news events (Meeter et al., 2010), whereas women tend to perform better on entertainment and arts questions (Howes and Katz, 1988). Interest in the media has consistently been shown to be the most influential demographic characteristic on public events memory performance (Meeter et al., 2010).

1.3.1.3.2 Measuring Autobiographical Memory

Owing to the variation in definitions of episodic memory, and the trend of associating episodic and autobiographical memory, it follows that different researchers have suggested different methods of measuring autobiographical memory. In the last ten years research on autobiographical memory has focused on dissociating the fact (semantic) and personal event (episodic) elements of autobiographical memory (Levine, 2002, Piolino et al., 2002, Piolino et al., 2007). Most recently researchers have attempted to build on this by investigating the autonoetic elements of personal events. Autonoetic elements of memories can be described as the subjective mental experience of the individual, in which they can feel like they are re-living the event when remembering it through processes such as vividness of the memory, visual imagery associated with the memory and emotional re-experiencing of the event (Irish et al., 2008). For both the autonoetic approach and the episodic/semantic elements approach

testing on a single occasion will provide the information required for analyses of memory function in terms of episodic/semantic and autonoetic/non-autonoetic components.

An earlier method of measuring autobiographical memory is to use the "Crovitz" or key word method, in which participants are given a set of words, often differentiated into emotionally positive, negative or neutral, and asked to produce a personal memory stemming from the given word (Crovitz and Schiffman, 1974). However, this method is often used without directing the subject as to what time of life the memories should come from (although they are asked to date the memory), meaning that complete periods of the person's life may be left out.

Another technique has been to ask for specific memories, in line with given themes such as employment, birthdays etc., from defined time-periods. Tests using this method include the (Kopelman) Autobiographical Memory Interview (AMI) (Kopelman, 1989), Borini's Autobiographical Memory test (Borini et al., 1989) and the Columbia AMI (McElhiney et al., 1997, McElhiney et al., 1995). These tests are usually used to analyse the amount and content of memories on a single occasion.

The main difference in memory tests described above is whether the goal is to examine the specificity of memories a participant in a clinical group can produce, compared to controls, or whether it is to examine consistency in autobiographical memory recall over more than one occasion. While many of the studies of autobiographical memory in depression have concentrated on the former goal, the purpose of the current research is the latter. A measure of consistency was chosen in the current study so that change over time could be assessed in a normal and depressed sample. In addition, using a measure of consistency with a sample of participants undergoing ECT allows for detection of any retrograde amnesia, or loss of previously

held memories. Thus, the method utilised in the current research is to record specific memories produced during a depressive episode and test how subsequent recall of the same memories is affected by the course and treatment of the depressive episode. A lack of normative data regarding consistency of recall on these instruments means that there is no way of knowing what scores qualify as being within the normal range of forgetting and what qualifies as an impairment in autobiographical memory recall. A limitation of this method is that it does not take recent theoretical components of autobiographical memory into account, in that it does not separate semantic and episodic facets of autobiographical memory, nor does it investigate autonoetic aspects of it. Despite these limitations, use of this method allows for assessment of consistency in autobiographical memory over time, and whether this is different for depressed participants and controls.

There is difference of opinion in current literature as to whether recalling the same memory repeatedly will strengthen or weaken retrieval on subsequent occasions. The traditional view of the memory consolidation theory has been that once a memory is entered into LTM is becomes stable and no longer open to disruption. However in recent years it has been proposed that the recalled memory exists in a fragile state following recollection, and open to distortion before being reconsolidated (Nadel and Hardt, 2011). If, as this suggests, memory becomes unstable after recall, this should have an equal chance of occurring across patient and control groups, and as such should not affect results of the current study. Measures like the Columbia AMI-SF have rarely been used to study memory function in normal populations, and although they have been used for control participants in clinical studies (Lisanby et al., 2000, McElhiney et al., 1995) limited results have been published in peer review journals, especially regarding the short-form of the test.

When studying autobiographical memory and public events memory, the question of which definition a researcher identifies with, and which measure they choose, will be determined by the purpose of the individual study. In the current research, as mentioned above, the primary aim is to assess long-term memory, in both public events and autobiographical memory, from one time-point to another. In this way it is not only the difference between groups that we are interested in, but also the change in performance from one time-point to another. As such, despite their limitations, general measurements of autobiographical memory and public events memory, such as the Columbia AMI and an Events Questionnaire, are suitable for the current research, without delving deeper into their conceptual divisions or definitions.

One reason for this is that having measures of verifiable general retrospective memory is of importance in clinical populations. In clinical situations it is important to have a measure of how much memory is lost from one time period to another. In particular these measures can be useful when measuring the impact of interventions such as Electroconvulsive Therapy (ECT), planned surgical interventions for epilepsy or cranial radiotherapy. When questionnaires are used in this way one important measurement is how much of the information known at baseline is retained at follow-up. In the same way, they can also be used to track changes in memory over the course of a progressive illness, such as Alzheimer's or Parkinson's disease, or an illness like depression where cognitive state may fluctuate. In order to adequately elucidate findings of autobiographical and public events memory questionnaires in these clinical groups it is important that we know how healthy controls perform over time on the same measures.

1.3.1.3.3 Consistency of retrospective memory

While studies of retrospective memory loss over long periods of time are found in neuropsychiatric and brain-injured groups, studies of memory loss/consistency over time in the normal population are sparse. Those that have examined this issue refer mainly to memory in aging and to the phenomenon of "flashbulb" memory, that being memory for highly unusual, emotive and well known world events, for instance the September 11th attacks (Brown and Kulik, 1977). The aging studies are generally based on one assessment of long-term memory from different life periods, where differing lengths of interval between current testing and the acquisition of the original memory are examined (Piolino et al., 2002). The time period assessed is often decades, and findings have shown that episodic memory is more likely to be lost over time than semantic memory, especially for more remote time-periods (Tulving, 1995, Piolino et al., 2002).

Studies of flashbulb memories usually assess specific memories on more than one occasion, and the first assessment usually occurs as soon as possible after the event. This allows for testing what happens to a memory from the time it is encoded, rather than a long time later, as is often the case in aging studies. One recent study has looked at recall of both personal and factual information related to the flashbulb event of the September 11th attacks, at baseline (8-21 days after the event) and one year follow-up in healthy adults, and found that while both types of memory decline at a similar rate in the first three months after encoding, personal memories of the event are more stable over longer periods of time than factual information (Budson et al., 2007). Another group examined memory for the September 11th attacks, as well as an autobiographical memory unrelated to the flashbulb event, and found that both the autobiographical and flashbulb event memories declined at the same rate, with a loss of approximately 33%

in consistency for each type of memory at one year follow-up (Talarico and Rubin, 2003).

This type of information is rarely available for studies using common types of autobiographical memory assessments, as mentioned above. Two studies have examined consistency over time in Public Events Questionnaires and reported significant correlations and moderate to high levels of consistency between time-points. However, one of these studies only assessed a small number of participants at one month follow-up (n=15) (Bizzozero et al., 2004), while the other had a only seven participants at follow-up (Squire et al., 1989). However, more studies need to be undertaken with healthy controls to ensure findings with clinical populations are explained in terms of normal rates of remembering.

1.4 Memory and depression

1.4.1 Anterograde Memory and Depression

Anterograde episodic memory has consistently been found to be impaired in depression, as measured by tests of immediate and delayed verbal and visual memory (Austin et al., 2001, Bearden et al., 2005, Douglas et al., 2011, Gallassi et al., 2006, Veiel, 1997, Zakzanis et al., 1998). Meta-analyses have shown delayed memory processes to be more affected than those of immediate recall (Kindermann and Brown, 1997, Veiel, 1997) and older participants to be more affected than younger groups (Thomas, 2008). However, others did not find a difference between depressed and control groups, during the acute phase, on measures of verbal learning and memory (Porter et al., 2003).

A recent meta-analysis has found that memory deficits are related to depression severity (McDermott, 2009). In line with this, studies have found that anterograde

memory performance improved in a remitted depressed group (n=28) to the level of healthy controls (n=23) (Weiland-Fiedler et al., 2004). Similarly, at 2 year follow-up remitted depressed patients (n=17) were found to perform at the same level as the control group, however the control group was only tested at baseline so the possibility of this finding being due to practice effects cannot be ruled out (Biringer et al., 2007). Another study showed that remitters (n=11) were significantly more improved than non-remitters at six month follow-up when compared to baseline on measures of verbal learning and memory (Gallagher et al., 2007). In contrast, on measures of verbal memory, one study found remitted patients at six months (n=33) to be impaired compared to controls performance at baseline (n=15), and showed no significant change from baseline (Gallassi et al., 2006). These findings would indicate that anterograde memory deficits may be trait markers in depression, whereas the previous studies indicated it may be state related. It is possible that the small numbers in these studies, as well as different tests employed to measure anterograde memory may be the reason for such contrasting findings.

1.4.2 Retrospective Memory and Depression

1.4.2.1 Autobiographical Memory

Investigation of retrospective memory in depression has mainly focused on autobiographical memory function, although some studies have included public events memory in their assessment. As mentioned above, most studies that have examined autobiographical memory have focused on the specificity of memories recalled in depressed groups compared to controls. A consistent finding in this area is that of overgeneral memory recall in depression (Sumner et al., 2010, van Vreeswijk and de Wilde, 2004, Williams et al., 2007), whereby recalled memories are of general events

rather than specific aspects of events. They often refer to extended events, such as being on holiday or going to college, rather than discrete events such as a trip taken on the holiday or an incident that happened in a college lecture one day, etc. (Williams et al., 2007). Overgeneral memory has been suggested to be a stable trait marker for depression as it has been found to persist in recovery (Brittlebank et al., 1993, Peeters et al., 2002).

In contrast, studies that examine the amount of autobiographical memory lost over the course of depression, and how this varies with treatment, are scarce. One study that used an autobiographical memory questionnaire (Borini et al., 1989) found depressed participants scored significantly worse on all time-periods of the autobiographical memory test compared to controls at baseline and that retrospective memory function in remitted depressed patients at six months (n=33) was still significantly impaired compared to controls performance at baseline (n=15) (Gallassi et al., 2006). It is noteworthy that, at the present time, no other study appears to have specifically studied consistency in autobiographical memory over the course of a depressive episode.

1.4.2.2 Public Events Memory

Despite the numerous findings of dissociation between autobiographical and public events memory as mentioned above, there is little research regarding public events memory in depression. Again, the phenomenon of overgeneral recall has been demonstrated (Warren and Haslam, 2007), possibly indicating a broad effect of overgeneral recall in retrospective memory in depression. An early study found that depressed participants showed no change in performance on a public events questionnaire from baseline to 7 month follow-up (Squire et al., 1981), however

numbers were very low in the depressed group (n=7), and diagnoses varied. Using a similar test, depressed participants (n=10) were found to have no change in amount of public events recalled at three week follow-up testing, compared to baseline (Calev et al., 1989). A more recent study used the verbal section of a historical events questionnaire, the MLT' 88 (Andreani et al., 1990), an Italian instrument that assesses long-term memory function using questions and pictures of historical events. The study showed no differences between controls (n=15) and a depressed group (n=42) during a depressive episode (Gallassi et al., 2006). The same study showed significant improvement in performance of depressed participants when remitted (n=33). Controls were not re-tested at six month and as such it is unclear whether this improvement was due to a practice effect. Also non-remitters were not tested due to the low number of non-remitters in that study. Again, the issue of consistency of retrospective memory for public events over the course of depression needs to be investigated further.

1.4.3 Summary - Cognition and Memory function in depression

Deficits in the acute phase of depression are apparent in effortful tasks of attention and, although attention improves with improvement in mood, deficits may remain relative to controls. For psychomotor function, depressed patients may be impaired relative to controls on reaction time, which is sensitive to depression severity. However, psychomotor function has been shown to return to the level of controls at follow-up. Executive impairments are found in the depressed phase and, although some studies have shown a significant increase in performance on remission, there may still be deficit at follow-up compared to controls. Anterograde memory is commonly found to be impaired in the depressed phase; however, mixed results have been found in remission. Public events memory has not been found to be impaired at baseline and follow-up

compared to controls. Finally, consistency of performance in autobiographical memory was shown to be significantly impaired in remitted depressed patients compared to controls at follow-up.

Despite increased interest and progress in research in this area in recent years many studies are still lacking in a healthy control group that is followed up at the same time-points as the depressed group. In addition, some studies still do not account for differences within the depressed population studied, such as depression type (e.g. unipolar/bipolar, psychotic/non-psychotic). Importantly, for longitudinal studies, the effects that passage of time may have on cognition in healthy controls needs to be elucidated further.

1.5 Treating Depression

1.5.1 Psychotherapy

A range of psychological and pharmacological treatments are commonly used to treat major depression. Psychological interventions for moderate depression include Cognitive Behavioural Therapy (CBT), Behavioural Activation, Interpersonal therapy (IPT), psychodynamic therapy, counselling, couples therapy and Rational Emotive Behavioural Therapy. Psychological interventions have been found to relieve depression and help towards long-term alleviation of the illness (National Institute for Clinical Excellence, 2009). A recent meta-analysis of randomised-controlled trials of psychological and pharmacological therapies in depression, showed that psychotherapy has a small but significant beneficial effect on depressive symptomology (Cuijpers et al., 2010). For mild to moderate depression, psychological intervention, in particular CBT or IPT, could be recommended as a treatment option, however for moderate to severe depression a combination of psychotherapy (IPT or CBT) along with an

antidepressant is the recommended treatment (National Institute for Clinical Excellence, 2009). In support of this, it has been shown that combined treatment is significantly more effective than pharmacotherapy alone and even more effective again than psychotherapy alone (Cuijpers et al., 2010), however others researchers have cautioned that more information about the benefits of combination therapies over monotherapy, is required (Frank et al., 2005).

1.5.2 Pharmacotherapy

Monoamine Oxidase Inhibitors (MAOI's) and Tricyclic Antidepressants (TCA's) were the first antidepressants to come into use more than half a century ago (López-Munoz and C., 2009). Currently there are 35 different individual preparations of antidepressant on the market, including Selective Serotonin Re-uptake Inhibitors (SSRI's), dual acting Serotonin and Noradrenaline Re-uptake Inhibitors (SNRI's) and Noradrenaline and Specific Serotonin antidepressants (NaSSa's) (National Institute for Clinical Excellence, 2009). In a series of reviews the relative benefits and side-effects of the different drug classes were explored and will be discussed briefly here (National Institute for Clinical Excellence, 2009). MAOI's work by binding irreversibly to monoamine oxidase, thus preventing the metabolism of noradrenaline and serotonin and increasing monoamine transmission. MAOI's may have serious side-effects that include a potentially dangerous rise in blood pressure if food or drinks containing tyramine are ingested, or drugs containing monoamines are taken concomitantly. TCA's inhibit re-uptake of monoamines thereby increasing neurotransmission of serotonin and noradrenaline. TCA's were found to be more effective in treating MDD than placebo, and equally as effective, but not as well tolerated, as other antidepressants. Side-effects

of TCA's include sedation and anti-cholinergic effects such as dry mouth, blurred vision, constipation, urinary retention and sweating. SSRI's inhibit re-uptake of serotonin into the presynaptic neuron, increasing serotonergic neurotransmission. They were found to be equally effective as other anti-depressants, well tolerated and safer in overdose. Side effects of SSRI's vary according to the type prescribed but in general headache, nausea and diarrhoea are most often reported. Newer dual-acting SNRI's such as Venlafaxine and Duloxetine have not been found to be more effective than other anti-depressants and side-effects include nausea, headache and a possible increase in blood pressure. Finally, Mirtazepine, a NaSSa, has not been found to be more effective than other classes of antidepressant and may cause weight gain and sedation (National Institute for Clinical Excellence, 2009).

1.5.3 Treatment Resistant Depression

Psychotherapy and pharmacotherapy are commonly employed as first line treatments in MDD. However, recent studies have shown that less than 40% of patients remit after the first treatment course with antidepressants, even when treatment is of adequate dose and duration (Rush et al., 2006). This figure falls to 30.6% after a second treatment course of either antidepressants alone or augmented with another drug or psychotherapy, 13.7% after a third course and 13% after a fourth course of antidepressants augmented by another medication. The authors note that after two steps of treatment remission is achieved in over 50% of patients; however, after this the chances of remission decline significantly (Rush et al., 2006). These results reveal that treatment resistance is an important problem when treating a major depressive episode. Combining pharmacotherapy with psychotherapy, as well as use of ECT have been proposed as strategies to increase remission rates (Shelton et al., 2010). Although it is known that if

someone has shown treatment resistance to pharmacotherapy they may also respond less well to ECT (Sackeim, 2001) the treatment may still be highly effective in treatment resistant populations, with more than 50% achieving remission after treatment (Khalid et al., 2008, Kellner et al., 2010a, Eranti et al., 2007).

1.6 Electroconvulsive Therapy

Electroconvulsive therapy (ECT), also known as Electroshock Therapy, is a highly effective treatment for depressive illness (UK ECT Review Group, 2003), especially in the case of severe and life-threatening depression and where improvements in the patient's condition are urgently required (National Institute for Clinical Excellence, 2009). However, despite its proven efficacy, ECT remains a somewhat controversial treatment. This controversy is partly due to the fact that a clear mechanism of action of ECT is still to be identified (National Institute for Clinical Excellence, 2003) as well as subjective complaints of memory dysfunction, in particular autobiographical memory loss, after treatment (Rose et al., 2003).

1.6.1 Development of ECT

ECT has been utilized in psychiatric treatment since the late 1930's. Origins of interest in the area of "shock therapy" is usually reported to have stemmed from studies of Hungarian neuropsychiatrist Ladislas Meduna in 1934, although others have noted that interest in the connection between seizures and behaviour change can be traced much further back. For example, it has been reported that the ancient Greeks had an interest in the effects of seizures on behaviour (Linington and Harris, 1988), while camphor-induced seizure therapy for psychosis was first reported by Melchior Adam

Weikhard in 1796 (Faedda et al., 2010). Meduna (1934) carried out post-mortem studies and noted that structural changes to nerve-endings in the brains of epileptic patients were almost the exact opposite of those found in patients with schizophrenia (Berrios, 1997). These findings fitted with the observations that epileptics rarely became psychotic and conversely that patients with schizophrenia rarely presented with epilepsy (Faedda et al., 2010), leading to the idea (now known to be incorrect) that schizophrenia and epilepsy were mutually exclusive: one could not occur in the presence of the other.

Thus, Meduna began to induce therapeutic seizures for psychosis using camphor oil (Meduna, 1934) and cardiazol (Meduna, 1935). At the time seizures, or "fits" as they were often referred to, were induced mainly through use of substances that were be inhaled, injected or ingested (Berrios, 1997). It was the work of two Italian researchers Cerletti and Bini (1938) that led to the development of safe electrically induced seizures in humans (Linington and Harris, 1988, Cerletti and Bini, 1938). By examining electrode placement, stimulus dosing, individual measures of electrical resistance, therapeutic effects by type of seizure, number of seizures necessary for therapeutic effects and seizure side-effects, Cerletti and Bini developed a safe and effective method of electroconvulsive therapy (Faedda et al., 2010).

1.6.2 Mechanism of action

Despite such a long history, the exact mechanism of action of ECT is still unknown. Earlier research suggested that ECT may lead to an increase in release of noradrenergic, dopaminergic, serotonergic and GABAergic neurotransmitters, which may contribute to antidepressant activity, in line with the monoamine hypothesis of depression, whilst inhibition of cholinergic systems may be responsible for memory changes (Rami-Gonzalez et al., 2001).

As mentioned in the discussion of neurobiological and neuroanatomical changes seen in depression (section 1.1.5) hippocampal volume has been shown to be reduced in depressed patients compared to healthy controls (Videbech and Ravnkilde, 2004). Animal studies have reported that electroconvulsive shock (ECS) in rats induced significant endothelial cell proliferation in the hippocampus (Frank et al., 2005) and a 10 to 30% increase in vascular density in one part of the hippocampus, the stratum lacunosum moleculare (Van der Linden and GREMEM, 2004).

More recently, studies have focused on neurotrophic changes in the brain in response to depression and antidepressant treatments, including ECT (Pittenger and Duman, 2008). Neurotrophic factors such as brain derived neurotropic factor (BDNF) and vascular endothelial growth factor (VEGF) have been shown to be up-regulated after treatment with ECS in animal studies, and the resulting levels of up-regulation are to a higher level than those found with antidepressant therapy (Warner-Schmidt and Duman, 2006). A recent paper suggests that there is a profound increase in the number of new neurons after just one session of ECS, with these neurons surviving up to two months later (Hanson et al., 2011). Furthermore, multiple sessions of ECS result in a large increase of neural progenitor cell proliferation, to a greater degree than after administration of fluoxetine (Madsen et al., 2000, Hanson et al., 2011).

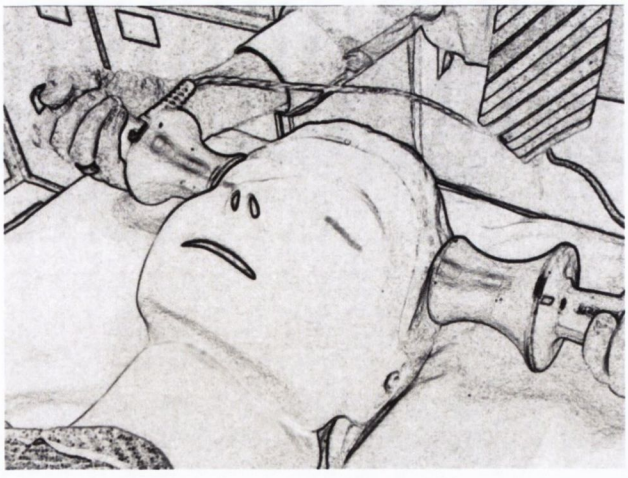
1.6.3 Administration

ECT can be used in severe depression, when a quick and effective treatment is required, and in moderate depression that does not respond to adequate treatment with medication (National Institute for Clinical Excellence, 2009). ECT can also be used in

emergency situations, involving patients who are extremely suicidal, severely depressed, or showing severe psychomotor retardation with associated dehydration or poor physical state (Royal College of Psychiatrists, 2005).

During a session of ECT a current of electricity is passed between electrodes on the patients scalp to elicit a generalised seizure in the brain (Kellner et al., 2010b). Short-acting anaesthetics, such as methohexital, propofol, etomidate or sodium thiopentone, and a short-acting muscle relaxant, succinylcholine, are administered before induction of a seizure to prevent injury and minimise discomfort associated with seizure induction (Kavanagh and McLoughlin, 2009).

A number of different electrode placement options have been developed for ECT, as illustrated in Figure 2. Placements fall into two common categories: bitemporal (BT) ECT and unilateral (UL) ECT. In standard BT ECT an electrode is placed on each temple and a current passed between the two. Bifrontal ECT is a less common form of bilateral placement, but one that is receiving renewed interest recently (Prudic, 2008, Dunne and McLoughlin, 2011). However, standard BT ECT remains the most common BT ECT placement (Kellner et al., 2010b). A recent study of ECT use in one region of Ireland showed that 83% of patients admitted for ECT over a five year period received BT ECT (Enriquez et al., 2010). For UL ECT electrodes are placed on one side of the head only, usually in the D'Elia position (D'Elia and Raotma, 1975). Electrode placement in UL ECT is usually on the non-dominant side of the head (usually right), to avoid the occurrence of side-effects to left-hemisphere functions such as language (Kellner et al., 2010b).



a.

b.

c.

Figure 2 Electrode placements during electroconvulsive therapy
(A) bitemporal, (B) bifrontal and (C) unilateral electrode placements

Seizure threshold (ST), the minimal electrical charge needed to produce a seizure of adequate clinical duration, may differ across patients and is found by titrating the dose upwards until an adequate seizure occurs (Sackeim et al., 1987). An adequate seizure can be defined as a tonic-clonic motor activity lasting at least 15 seconds, or at least 25 seconds as monitored by EEG (Shapira et al., 1998, Kavanagh and McLoughlin, 2009). For therapeutic efficacy treatment is given above the ST, usually 1.5 times ST for BT ECT. Research on UL ECT has found low and moderate doses (0.5 to 2.5 times ST) are not as efficacious as BT ECT (Sackeim et al., 1993, Sackeim et al., 2000) but high dose (6 X ST) right UL (RUL) ECT is (Sackeim et al., 2000, Kellner et al., 2010a).

Wave form and pulse width of electrical stimulation have been studied in relation to promoting efficacy of treatment and different forms have been used to date (see Figure 3). The shortest duration of electrical stimulus needed to stimulate a neuron for adequate seizure response is 0.1 to 0.2 milliseconds (Prudic, 2008). Sine wave electrical stimulation was originally used in ECT, however studies have shown that it provides much more electrical charge than necessary, compared to brief pulse stimulation (Prudic, 2008) and no benefit for sine wave over brief pulse has been found (UK ECT Review Group, 2003). As a result, brief pulse ECT is now recommended (Royal College of Psychiatrists, 2005). Brief pulse stimulation provides 0.5 to 2 milliseconds duration of electrical charge, which is still more than necessary for induction of a seizure. Interest in ultra-brief pulse stimulation has been renewed recently (Sackeim, 2004, Sackeim et al., 2008) as it delivers less electrical stimulus than brief pulse stimulation (less than 0.5 milliseconds pulse width), however studies of its efficacy are on-going.

Frequency of treatment has been examined in relation to optimal treatment response. In Europe the standard is for treatment to take place twice a week, whereas in

the United States treatment three times per week is common (Lerer et al., 1995). Treatment response at the end of a course is equivalent for each frequency, although three times weekly produces a more rapid response than twice weekly (Lerer et al., 1995, Shapira et al., 1998) but has been shown to produce more cognitive side effects than twice weekly (Lerer et al., 1995, Shapira et al., 1998). Two recent meta-analyses of twice versus thrice weekly ECT have found that twice weekly treatment has a similar efficacy profile to thrice weekly (UK ECT Review Group, 2003, Charlson et al., 2011).

A recent report from the Mental Health commission in Ireland (MHC) found that prescription of ECT in Ireland varied according to region (Mental Health Commission, 2009). However, give that these findings were based on the area of the treatment centre, and not the patients' county of origin, the data were re-analysed and it was found that regional variation in patients receiving ECT is not as skewed as previously reported (Dunne and McLoughlin, 2012). A previous report on ECT variation within Ireland found that the admitting diagnosis, patient turnover and psychiatrist attitude towards ECT was correlated with ECT prescription (Latey and Fahy, 1988).

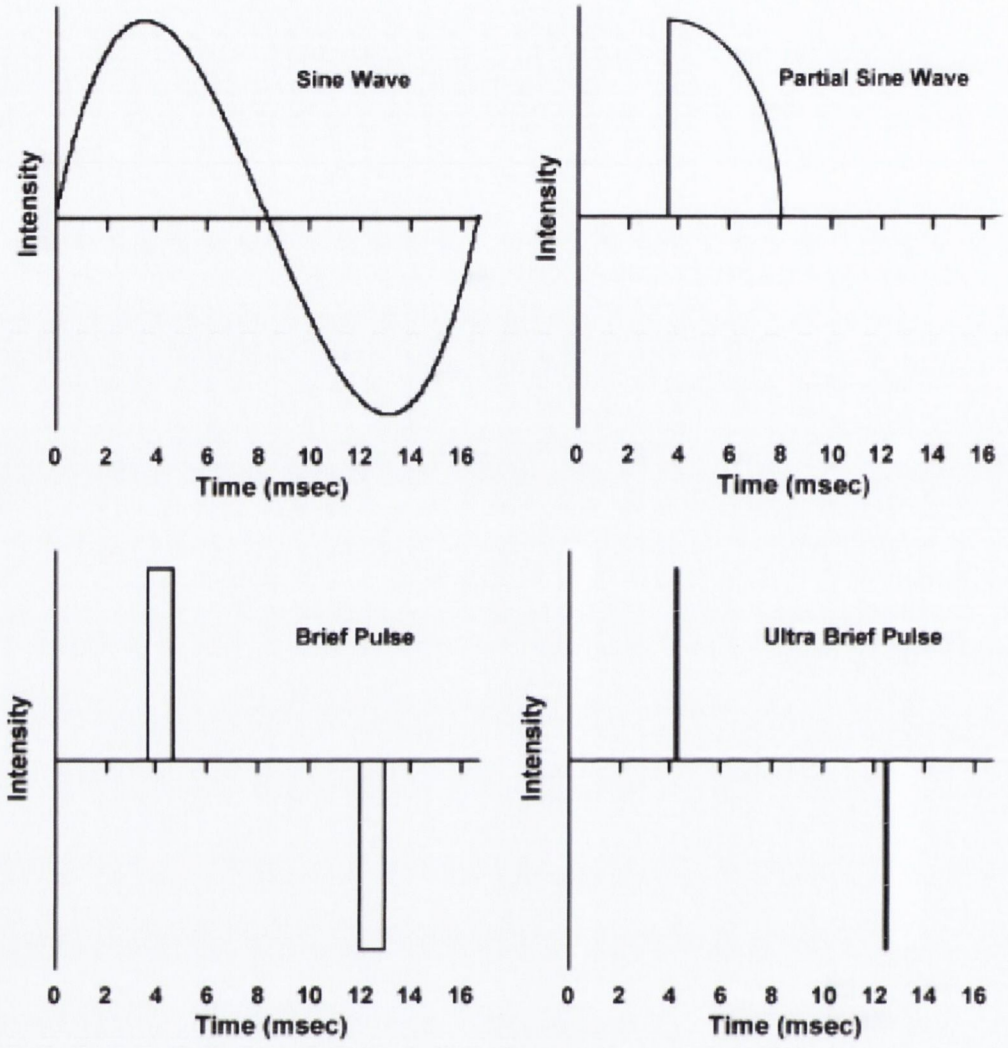


Figure 3 Waveforms used in ECT
Clockwise from top left: sine wave, partial sine wave, ultra brief pulse and brief pulse

(Sackeim, 2004)

1.6.4 Cognition and ECT

Cognitive side-effects of ECT are often reported, and most research has concentrated on acute and sub-acute effects of ECT, a timeline that ranges from a few days after the final treatment, to two weeks after end of treatment. Fewer studies have investigated longer-term cognitive outcomes after ECT, although this area has been investigated more often in recent years. In keeping with the depression literature described above, the focus here will be on attention, psychomotor performance and executive function, before moving on to a discussion of memory side-effects arising from ECT.

1.6.4.1 ECT and Attention

A recent meta-analysis of studies involving objective assessment of cognitive function before and after ECT has shown that performance in the domain of attention, on digit span forward and spatial span, does not change from pre-treatment to two weeks post-ECT, however a small increase in performance was shown for mental control variables (Semkovska and McLoughlin, 2010). This finding is in line with others who have found no difference after three treatments (Porter et al., 2008b), seven treatments (Calev et al., 1989), one month post-ECT (Ng et al., 2000) and six months post treatment (Sackeim et al., 2007) on performance in tasks involving attention. However, some studies have reported an improvement in attention at end of treatment compared to baseline (Sackeim et al., 2007), while others report worsened performance in visual attention in patients receiving right unilateral ECT (Rogers et al., 2002). Working memory is often included in the literature pertaining to attention and has been shown to improve from pre-treatment to two weeks post-treatment (Semkovska and McLoughlin, 2010).

1.6.4.2 ECT and Psychomotor Processing

Changes in psychomotor speed and processing speed before and after ECT have also been examined. Some findings have indicated a deficit in psychomotor and processing speed at end of treatment (Neylan et al., 2001, Sackeim et al., 2007, Tsourtos et al., 2007). However, others have challenged this finding, showing no change from baseline to end of treatment on the Trail Making Test part A (TMT A) (Dubovsky et al., 2001). These findings are broadly in line with a meta-analysis showing no change between pre- and post-performance on the TMT A, and small deficits in other measures of psychomotor speed at end of treatment (Semkovska and McLoughlin, 2010). However, some have shown an improvement in processing speed post-ECT (Bosboom and Deijen, 2006). Performance has been shown to recover to pre-treatment levels within two weeks (Semkovska and McLoughlin, 2010) and has been found to be comparable to that of controls at four to six weeks post-treatment (Tsourtos et al., 2007). Studies have also shown significant improvements in psychomotor and processing speed after three and six months (Dubovsky et al., 2001) and one year (Bosboom and Deijen, 2006). However others have found no improvements in the long-term compared to baseline (Sackeim et al., 2007).

1.6.4.3 ECT and Executive Function

The executive functions have also been examined in relation to ECT. Studies have shown significant impairment in verbal fluency tests at end of treatment, relative to baseline (Dubovsky et al., 2001) and healthy controls (Pendleton Jones et al., 1988). This has also been shown after one session of maintenance ECT (Datto et al., 2001).

In the case of persisting executive deficits, some have shown a significant improvement from end of treatment to follow-up, resulting in performance at or above

baseline levels at six months (Dubovsky et al., 2001), while others have shown no significant improvement in relation to baseline score (Pendleton Jones et al., 1988), however this study had low numbers (n=10) and mixed waveforms and electrodes placements were used but not differentiated between. Two recent systematic reviews found medium to large impairments at end of treatment, which recover to baseline levels within two weeks and either show slight improvement or no improvement above baseline levels in the long-term (Semkovska and McLoughlin, 2010, Ingram et al., 2008).

1.6.5 Memory and ECT

Learning and memory have been extensively studied in relation to ECT, primarily due to patients reporting memory difficulties during and after treatment (Rose et al., 2003). Both anterograde and retrograde memory have been assessed, and will be discussed separately here.

1.6.5.1 Anterograde Memory and ECT

Anterograde memory is often split into verbal and visual functions, as well as immediate memory (learning) and delayed recall. It has been shown by various researchers that immediate verbal memory is impaired during and at the end of a course of ECT, compared to pre-treatment levels (Neylan et al., 2001, Ng et al., 2000, Frasca et al., 2003, Sackeim et al., 2007). However, others have shown no change in learning ability from baseline to end of treatment (Zervas and Jandorf, 1993). Regarding long-term outcome, immediate verbal recall has been shown to return to normal within a few days of finishing treatment (Ingram et al., 2008), and may improve beyond pre-treatment levels at one month (Ng et al., 2000) and six month follow-up (Sackeim et al.,

2007). Delayed verbal memory may be impaired both during and in the first few days after a course of ECT, as compared to baseline functioning. Studies have found a significant decrease in delayed verbal memory after six treatments (Neylan et al., 2001, Ng et al., 2000) and at end of treatment (Sackeim et al., 2007, Ng et al., 2000, Zervas and Jandorf, 1993). Delayed verbal recall has been shown to improve significantly above baseline levels, at one month and six month follow-up (Sackeim et al., 2007, Ng et al., 2000). However, some have found verbal memory to remain impaired at six months follow-up compared to healthy controls (Criado et al., 2007). A recent meta-analysis found delayed verbal recall showed small to medium improvements or a return to baseline functioning from two weeks post-treatment (Semkovska and McLoughlin, 2010).

Visual memory can also be tested for immediate and delayed recall. Studies investigating immediate recall of visual information have found significantly lower recall at post-treatment assessment compared to baseline (Calev et al., 1991, Ng et al., 2000). In contrast, others have shown no change in immediate visual memory from pre-treatment to end of treatment (Calev et al., 1989). Some studies have found a persisting impairment at one month (Ng et al., 2000), whereas others have shown significant improvement from baseline at six month follow-up (Sackeim et al., 2007, Calev et al., 1991). Findings are also mixed for studies of delayed visual recall, with some authors finding no change from pre to post-treatment (Calev et al., 1991, Ng et al., 2000) and others showing an impairment at end of treatment compared to baseline (Sackeim et al., 2007). Regarding long-term outcomes, delayed visual memory has been found to improve significantly from baseline at six month follow-up (Sackeim et al., 2007). Reviews of the area have suggested that verbal memory processes may be more affected

than visual processes after ECT, and delayed recall seems to be more impaired than immediate recall (Ingram et al., 2008, Semkovska and McLoughlin, 2010)

1.6.5.2 Retrograde amnesia and ECT

Retrograde amnesia after ECT treatment has been studied extensively, as loss of memory for previously experienced events is a common complaint of patients after treatment (Freeman and Kendall, 1980, Rose et al., 2003). Retrograde memory has been studied based on objective memory questionnaires, as mentioned above, as well as through assessment of the patients' subjective experience of the treatment such as the Squire Subjective Memory Questionnaire (Squire et al., 1979). In the current study the focus is on objective memory impairment only and, as such, subjective memory outcomes will not be discussed further here.

1.6.5.2.1 Autobiographical Memory and ECT

In particular, autobiographical memory is reported to be impaired after ECT treatment. This has been demonstrated since the earliest studies of cognitive outcomes in ECT (Stieper et al., 1951). Deficits in autobiographical memory have been consistently reported at end of treatment as compared to pre-treatment levels (Calev et al., 1991, Lerer et al., 1995, Lisanby et al., 2000, McCall et al., 2000, Sackeim et al., 1993, Sackeim et al., 2000, Sackeim et al., 2007, Sackeim et al., 2008, Squire et al., 1981) and to healthy controls (Lisanby et al., 2000, Weiner et al., 1986). Findings regarding persisting deficits after ECT have been less clear-cut. Some studies have reported no deficits in autobiographical memory compared to pre-treatment levels, at one month and six month follow-up (Calev et al., 1991, Lerer et al., 1995). A recent study reported that patients treated with ultra-brief pulse ECT had no impairments at

two and six month follow-up (Sackeim et al., 2008). In contrast, others have found evidence of persisting deficits in autobiographical memory at various time-points. For example, decreased autobiographical memory recall has been shown, relative to baseline, at two months (Sackeim et al., 1993, Sackeim et al., 2008), six months (Sackeim et al., 2007, Sackeim et al., 2008), seven months (Squire et al., 1981) and three years (Squire and Slater, 1983) post-treatment. One study showed that at six month follow-up, patients continued to perform worse than both their own pre-treatment levels and those of healthy controls tested at the same time-points (Weiner et al., 1986). This is in contrast to more recent findings that showed the amount of persisting inconsistency in autobiographical memory to be the same for patients at two month follow-up as that found in controls at the same time-point (Lisanby et al., 2000). This is a noteworthy finding because some studies may simply report that clinical groups have decreased memory performance at follow-up, without investigating whether healthy controls actually show the same decrement, thereby indicating there is a problem where there may in fact be none. In addition, another study noted that the impairment found in recent autobiographical memory at three year follow-up had been present at baseline and may have been due to poor encoding during the depressive episode rather than the ECT treatment (Squire and Slater, 1983). Finally, it should be noted that for certain autobiographical memory measures performance cannot be better than baseline level, and so a return to baseline is the highest achievable state of functioning in some studies.

1.6.5.2.2 Public Events Memory and ECT

Public events memory has also been studied as a form of retrograde amnesia after ECT treatment. Studies have shown deficits in memory for public events before ECT treatment, as compared to controls (Meeter et al., 2011), and at the end of

treatment, as compared to pre-treatment performance (Calev et al., 1991, Lerer et al., 1995, Lisanby et al., 2000, Meeter et al., 2011, Sackeim et al., 2000, Sackeim et al., 2008) and healthy controls (Lisanby et al., 2000, Weiner et al., 1986). Studies have reported improvement to pre-treatment levels at one, three and six month follow-up (Weiner et al., 1986, Lerer et al., 1995, Meeter et al., 2011) as well as significant improvement above baseline functioning at six months (Calev et al., 1991). However, a recent study, using a technique assessing the amount of details recalled, rather than individual events, found memory for public events remained impaired relative to controls at two month follow-up (Lisanby et al., 2000). Nevertheless, in the same study overall public events memory had still improved at two months compared to end-of-treatment and was not significantly different to baseline performance at follow-up.

1.6.6 Parameters of ECT and cognition

Because of concern regarding cognitive side-effects of ECT researchers have investigated whether certain aspects of treatment could be the cause of these impairments and how best to alleviate them. Efforts have focused on placement of electrodes, waveform, pulse width, stimulus dosage and anaesthetic used in administration of the treatment, as well as number and frequency of treatments received.

1.6.6.1 Electrode placement and stimulus dosage

Different combinations of electrode placement and stimulus dosage have been developed to promote efficacy of ECT while simultaneously decreasing cognitive side effects. Earlier studies examined dosage at or just above ST, in RUL compared to BT electrode placement. Findings showed RUL ECT produced less cognitive deficits than BT ECT, but resulted in less therapeutic efficacy (Sackeim et al., 1987). Increasing

stimulus dosage for RUL ECT was attempted next but at low doses (2.5 times ST) although less cognitive deficits than BT ECT were found efficacy still remained lower for RUL ECT (Sackeim et al., 1993). Further to this, it has been shown that as stimulus dose increases for RUL ECT, so do the cognitive effects (Ingram et al., 2008). For example, a recent large-scale prospective study examined efficacy and cognitive side-effects of BT ECT at 1.5 times ST, compared to RUL ECT at low-dose (0.5 X ST), moderate-dose (1.5 X ST) and high dose (5 X ST) (Sackeim et al., 2000). The authors noted that as stimulus dosage increased for RUL ECT, the cognitive deficits also increased.

A number of studies have found that cognitive effects are significantly greater with BT ECT than high-dose RUL ECT post-treatment (Sackeim et al., 1993, Sackeim et al., 2000, Sackeim et al., 2007, Sackeim et al., 2008) and at two month follow-up in the domains of autobiographical memory and public events memory (Sackeim et al., 2000) and verbal learning and autobiographical memory at six month follow-up (Sackeim et al., 2007). These results are similar to findings from a recent meta-analysis of electrode placement and stimulus dosage that found RUL ECT results in less cognitive side-effects up to three days post treatment than BT ECT in delayed verbal memory and autobiographical memory, however no significant differences were seen between RUL and BL ECT after three days post-treatment (Semkovska and McLoughlin, 2010). In addition, the authors noted that increased stimulus dosage resulted in a decrease in verbal learning and delayed retrieval, visual recognition and semantic memory (Semkovska and McLoughlin, 2010).

1.6.6.2 Number and Frequency of treatments

The number and frequency of treatments received has also been investigated and results have shown that an increased number of ECT treatments is related to increased cognitive impairment (Sackeim et al., 2007, Sackeim et al., 2008). Increased frequency of treatment, that is, three times versus twice weekly, has also been found to have an adverse effect on cognitive function (Lerer et al., 1995, Shapira et al., 1998).

1.6.6.3 Anaesthetic and medications

Choice of anaesthetic has recently begun to take into account possible neuro-protective benefits of the drug used, which may alleviate or guard against cognitive impairment (MacPherson and Loo, 2008). This area needs further investigation but emerging anaesthetic targets are ketamine and short-acting opiates (MacPherson and Loo, 2008). Medication has also been studied both for its influence during ECT treatment and afterwards for maintaining therapeutic benefits. In general, medication such as TCA's, SSRI's, and anti-psychotics are thought to be safe during ECT, although some SSRI's may prolong seizure duration (Baghai et al., 2006). Use of anti-convulsants and mood stabilisers such as lithium may increase risk for delirium following ECT treatment (Merkl et al., 2009).

1.6.7 Summary - Cognition and Memory Function in ECT

Overall, findings regarding the cognitive side-effects of ECT have been mixed. In general, no change has been shown in attention after ECT, and attentional function may improve in the long-term. Psychomotor function shows either no change, or a small deficit, at end of treatment. There are some reports of improvement in the long-term;

however, others report no change from baseline. Regarding executive functioning, decreases in performance have been shown at end of treatment followed by recovery to pre-treatment level, and subsequent improvement above it. However, others have shown no improvement in executive function over time. Mixed findings have been demonstrated for verbal and visual memory, both in the acute phase and in follow-up. Autobiographical memory is consistently shown to be impaired at end of treatment testing compared to baseline and healthy controls. Findings are mixed regarding persisting deficits with some authors reporting no deficit at follow-up, while others have found impairments up to three years after ECT. Public events memory has been found to be impaired after treatment compared to baseline levels and to controls. Again, while some have reported no deficits at follow-up, one study has reported ECT patients as improved in performance on public events memory but still impaired relative to controls at two months follow-up.

In terms of electrode placement and stimulus dosage patients treated with BT ECT have been found to perform worse than those treated with high dose RUL on measures of delayed verbal memory, public events memory and autobiographical memory, both in the days post treatment and up to six months after treatment.

1.7 Overall summary

Cognitive impairment is a common feature of depressive illness and may also occur as a side-effect of treatment with ECT for the depressive episode. ECT-related cognitive impairment seems to be less severe with high-dose RUL ECT than the standard BT ECT, while maintaining the same efficacy. What is not clear at present is whether cognitive impairments in depression are state or trait phenomena. Longitudinal

studies may provide information as to how cognitive functioning changes over the course of a depressive episode. However it is necessary to interpret findings in terms of how healthy controls may change in performance on the same cognitive measures over the same amounts of time. This will ensure that normal changes in cognition are not interpreted as pathological changes in cognitive functioning. Similarly, it is not clear how long-term impairments in cognition after ECT relate to persisting deficits in non-ECT treated depression. Finally, consistency in retrospective memory function has rarely been studied in normal and depressed populations, and as such requires investigation.

1.7.1 Aims of the current research

By examining findings from the same assessments in healthy controls, depressed pharmacotherapy treated patients, and ECT treated patients, it is hoped that the effects of time, depression and ECT type on cognitive function can be unravelled. In addition, the cognitive deficits both immediately and up to six months after ECT therapy can be discussed in light of findings in a pharmacotherapy treated depressed group, thus giving a better indication of the relative severity of ECT-induced cognitive deficits.

The objectives of this research were:

1. To carry out a prospective case-control study of general cognition and retrospective memory function (The Mem-Dep Study) in unipolar depressed patients and healthy controls, that examined:
    a. The acute effects of a depressive episode on general cognition and retrospective memory
    b. Within group recovery of function in the depressed group at 2 month follow-up.

c. Longitudinal outcomes at six and 12 months follow-up of depressed patients compared to controls.

2. To examine the effect of ECT upon general cognition and retrograde memory in a sub-group of depressed patients in the EFFECT-Dep Randomised Controlled Trial (RCT), which examines the efficacy and side-effects of standard-dose bitemporal ECT compared to high-dose unilateral ECT, at end of treatment, three month and six month follow-up compared to pre-treatment performance.

1.7.2 Hypotheses

It was hypothesised that:

1. At baseline, autobiographical memory function will be worse in depressed participants than healthy controls, whereas public events memory function will be equivalent for both groups.
2. At baseline depressed participants will perform worse than controls on measures of attention, executive function and psychomotor speed and processing.
3. Performance on measures of retrospective memory and general cognitive function will improve over time as depression severity decreases.
4. At 12 months retrospective memory function and cognition will be at the same level as controls in patients who remit and remain well.
5. Patients who received high-dose RUL ECT would experience less retrograde memory and cognitive impairments than those who received standard-dose BL ECT.
6. Public events memory would be less affected by ECT treatment than autobiographical memory.

CHAPTER 2: MATERIALS AND METHODS

2.1 MATERIALS

2.1.1 Diagnostic assessment and baseline information

2.1.1.1 Background information

Background demographic information was collected at baseline for each participant (Appendix 1). This included name and address, marital status, date of birth, age, contact telephone number, educational attainment, main occupation and related socioeconomic group (professional, managerial and technical, manual and non-manual skilled occupation, partly skilled and unskilled occupations), height and weight. Information regarding current and previous illness was also recorded, which included information regarding previous depressive episodes, previous electroconvulsive therapy (ECT), date of last ECT, and source of referral (St. James's Hospital, St. Patrick's Hospital or St. Edmundsbury Hospital). Current habits regarding alcohol intake and smoking were recorded along with any family history of mental illness. Details of a next of kin were also gathered at this time and included name, address, telephone and email contact details.

2.1.1.2 Structured Clinical Interview for the Diagnostic and Statistical Manual, Axis 1

The research version of the Structured Clinical Interview for the Diagnostic and Statistical Manual for Mental Disorders, Axis 1 (SCID-I (First et al., 1995)) was used to confirm a diagnosis of major depression. The SCID-I (Appendix 2) is a semi-structured interview questionnaire used for diagnosing psychiatric disorders in line with the Diagnostic and Statistical Manual for Mental Disorders, fourth edition (DSM-IV). The

SCID has become the standard assessment instrument for diagnosing presence of axis 1 DSM-IV disorders (Zanarini et al., 2000). It consists of an overview section that includes demographic and employment history, current complaint, history of psychiatric illness, treatment history and current functioning, as well as nine diagnostic sections for Mood Episodes, Psychotic Symptoms, Psychotic Disorders Differential, Mood Disorders Differential, Substance Use, Anxiety, Somatoform Disorders, Eating Disorders and Adjustment Disorders (Rush et al., 2008). The questionnaire is designed so that diagnostic sections may be used alone or in conjunction with others. The research version of the SCID also includes a variety of disorder subtypes and specifiers that can be used to focus on a particular disorder of interest (Rush et al., 2008).

The Mood Episodes diagnostic section is the only section used in the current research as all participants are required to have a diagnosis of depression and takes approximately 15-20 minutes to administer. The questionnaire contains both probe questions and supplemental questions around each commonly seen symptom associated with depression. The interviewer rates each item in the diagnostic criteria independently on the basis of answers to the probe questions. Criteria are scored on three levels: a score of one indicating the criterion is absent or false; a score of two indicating that symptoms are sub-threshold; and a score of three is given when symptoms are at threshold level or above. Diagnosis is made both on lifetime prevalence and the most recent month.

Most evidence for reliability of the SCID is based on the version for the DSM-III and reports good overall reliability and test-retest reliability (kappa (κ) >0.70) for major depressive episodes (Rush et al., 2008). Fair-to-good test-retest reliability (κ = 0.61) and excellent inter-rater reliability (κ = 0.80) were found for the SCID for DSM-IV in depressed groups (Zanarini et al., 2000). Few studies have examined the validity

of the SCID, however one study found high positive predictive value of the SCID with a sample of mentally ill homeless participants, but low negative predictive value (Rush et al., 2008).

2.1.1.3 Treatment Review

A Treatment Review form (Appendix 3) was developed for use in the current research. Details of medications at baseline and follow-up time-points were recorded. This included dosage and number of times taken across the day, length of time at current dosage and compliance. This information was used to monitor changes in medication across the follow-up period.

2.1.1.4 The Antidepressant Treatment History Form

The Antidepressant Treatment History Form (ATHF-Appendix 4) was used to assess if the depressive episode met criteria for treatment resistance. The ATHF was originally designed by Harold Sackeim and colleagues in Columbia University, New York, USA, (Sackeim et al., 1990) and later updated (Oquendo et al., 1999) in order to provide an instrument that would clearly describe adequacy of treatment for the current episode and, in doing so, effectively evaluate treatment resistance. In the current thesis the ATHF was used to document medications received during the current depressive episode and to provide an indication of whether the participant was treatment resistant. It is estimated that 20% to 40% of depressed patients may be treatment resistant at the first episode (Sackeim, 2001) and treatment resistant patients who require several treatment steps have been shown to have higher relapse rates than those who respond to treatment earlier (Rush et al., 2006). ECT has also been found to be sensitive to

treatment resistance (Sackeim, 2001). In addition, in depression not treated with ECT, treatment resistance may predict response to future treatment.

The authors note that there are four key issues that must be taken into account when assessing treatment resistance in depression: ensuring that maximal therapeutic dosage is achieved; adequate duration of treatment at maximal and sub-maximal level; patient compliance; and the clinical outcome of treatment. On this basis, many patients are thought to be under-treated and do not receive adequate treatment trials (Sackeim et al., 1990).

The ATHF contains three sections. The first section deals with key issues pertaining to length of episode, type of depression (psychotic/ non-psychotic), previous ECT, and source of information in completing the ATHF (patient interview, pharmacy record, family interview, prescribing physician/therapist), which is rated on a scale from one to five with reference to its reliability (a higher score indicates better reliability). The second section records information regarding medication trials for the current episode. This documents the list of medications received in the current episode, blood levels (if measured) and daily dosage of medication, dates commenced and ceased, duration at each dosage, reason for change (including limiting side-effects) and clinical outcome. All antidepressants, mood stabilisers, benzodiazepines, typical and atypical neuroleptics are listed. The final section rates the adequacy of each separate medication, or combination of medications for each treatment trial. Combination trials include simultaneous use of lithium and antidepressants to non-psychotic patients or simultaneous use of antipsychotics and antidepressants to patients with psychotic features.

All documented medication trials are rated according to strict guidelines and each medication is rated separately. The guidelines provide scores for each trial, based

on duration and dosage, as follows: all trials of less than four weeks score 1; medications without established efficacy score 1; medications with uncertain efficacy score 2; selective heterocyclic antidepressant blood-level takes precedence over oral dosage; evidence of non-compliance diminishes the therapeutic trial strength; abandoning the trial due to side-effects where there is evidence of improvement diminishes the trial strength; and in combination trials each medication is rated separately. Scores range from 1 to 4, according to strict criteria for each medication, and a score of 3 or higher indicates that adequate dosage at a minimum duration of time has been administered. Thus if the patient has not improved with this adequate treatment (scores of ≥ 3) they are deemed treatment resistant.

Studies that have used the ATHF have noted strong inter-rater reliability of the instrument (Sackeim et al., 1990, Prudic et al., 1990). Good predictive validity for short-term clinical outcome (Prudic et al., 1990) and relapse after ECT (Sackeim et al., 1990, Shapira et al., 1995) have also been documented.

2.1.2 Clinical Assessments

2.1.2.1 The Hamilton Depression Rating Scale, 24-item version

The Hamilton Depression Rating Scale 24-item (HDRS-24-Appendix 5) was used to assess severity of depression at baseline and follow-up time-points. The HDRS was originally designed to assess severity of depressive symptoms in patients with a primary depressive illness and is now the most commonly used measure of depression severity (Williams, 2001). It was first published in a 17-item format with the optional addition of four items making up the 21-item version (Hamilton, 1960, Hamilton, 1967); however it was recommended to only score the original 17-items as the last four (diurnal variation, depersonalisation/derealisation, paranoid symptoms and

obsessive/compulsive symptoms) did not describe illness severity. Despite this suggestion, many researchers have used both extended and shortened versions of the HDRS, with at least 20 different versions having been used in published studies (Bagby et al., 2004). In this research we use the 24-item HDRS (Kovacs et al., 1981) which includes additional questions on helplessness, hopelessness and worthlessness.

Although widely used, the lack of standardised administration and scoring has led to concerns regarding the reliability of the instrument (Williams, 2001). In an effort to address this problem, standardised instructions were published by several authors, the most widely used of which is the Structured Interview Guide for the Hamilton Depression Rating Scale (SIGH-D) (Williams, 1988). Use of the SIGH-D was shown to improve item-reliability of the HDRS, and is used in the current research. A recent systematic review of studies using the HDRS in clinical research found that scores on internal reliability (Cronbach's alpha 0.46 to 0.97), inter-rater reliability (r = 0.82 to 0.98, intraclass co-efficient (ICC) = 0.46 to 0.99) and test-retest reliability (r = 0.81 to 0.98) were good (Bagby et al., 2004). Similarly, levels of convergent, discriminant and predictive validity were found to be acceptable by the same authors. This study did note, however, that at item level the test-retest coefficients and inter-rater reliability were weak for some items. This issue was addressed in the current research by conducting inter-rater reliability assessments for the HDRS-24 every six months (see methods section 1.2.3.1).

2.1.2.2 The Beck Depression Inventory, Version II

The Beck Depression Inventory, version two (BDI-II-Appendix 6) (Beck et al., 1996), was used as a measure of subjective depression severity. The BDI-II measures behavioural manifestations of depression in adolescents and adults, and was designed to

standardise assessment of depression severity and monitor change over time. It is also used to describe the illness. The original BDI (Beck et al., 1961) was based on observations of depressed patients during psychoanalytic therapy, and is organised around core symptoms commonly seen in depression. A series of statements of differing value were attached to each symptom, and participants were instructed to circle the number beside the statement which applied to them most over the previous two weeks. The numbers beside each circled statement were then summed for the total score. The questionnaire was updated in 1996 to reflect changes in criteria for a major depressive episode, as outlined in the DSM-IV (American Psychiatric Association, 2000), and to simplify the wording. The updated version contains 21 sets of symptoms and takes approximately five to ten minutes to complete.

The BDI-II has been found to have good item-total correlations of r = 0.5 to 0.7 (Beck et al., 1996). Internal consistency of the BDI-II has been shown to be high with a Cronbach's alpha of 0.93 in students, 0.92 in outpatients and 0.94 in primary care patients (Beck et al., 1996, Arnau et al., 2001). With regard to validity, good convergent validity has been shown between the BDI-II and the HDRS (r = 0.71), while discriminant validity of the BDI-II has been found to be fair-to-good between the BDI-II and Beck Anxiety Inventory (r =0.60) (Beck et al., 1988) and the BDI-II and the Hamilton Anxiety Rating Scale (r = 0.47) (Hamilton, 1959) according to the Beck et al study (1996).

2.1.2.3 The Brief Psychiatric Rating Scale

The Brief Psychiatric Rating Scale (BPRS-Appendix 7) (18-item) was used to screen for psychotic symptoms and as a secondary measure of depression type (psychotic/non-psychotic). The authors describe it as a rapid evaluation technique suited

to evaluation of patient change (Overall and Gorham, 1962). The original 16 item scale was published in 1962 and was based on the Lorr Multidimensional Scale for Rating Psychiatric Patients (Lorr, 1953) and the Inpatient Multidimensional Psychiatric Scale (Lorr et al., 1962). An 18-item version was later published (Overall and D.R., 1988) and is the most commonly used version. The BPRS includes symptoms common to a range of psychiatric disorders including schizophrenia and severe depression. The 18 symptoms covered are: Somatic Concern; Anxiety; Emotional Withdrawal; Conceptual Disorganisation; Guilt; Tension; Mannerisms and Posturing; Grandiosity; Depression; Hostility; Suspiciousness; Hallucinations; Motor Retardation; Uncooperativeness; Unusual Thought Content; Blunted Affect; Excitement; and Disorientation. Each symptom is rated for the last week and on a scale from one to seven. The total score is the sum of the scores from each of the questions.

The BPRS is not intended for use as a diagnostic instrument but as a brief and easy to administer probe for psychotic symptoms. The authors recommend using the BPRS as part of an 18-minute interview in which three minutes should be spent developing a rapport with the patient, ten minutes in non-directive questioning to elucidate answers to most of the questions and five minutes of direct questioning at the end to obtain any outstanding ratings.

In a review of studies using this measure the inter-rater reliability was found to have an ICC >0.8 in most studies (Hedlund and Vieweg, 1980). When items were divided into positive and negative psychotic symptoms the internal reliability of the BPRS was found to be good, with Cronbach's α scores of 0.81 and 0.91 reported (Nicholson et al., 1995). Good convergent validity was also reported between positive and negative items on the BPRS and the Positive and Negative Symptoms Scale (PANSS) (Kay et al., 1994), (Bell et al., 1992). Good concurrent validity was also noted

for the BPRS and the HDRS (Hedlund and Vieweg, 1980). In light of this, in the current research only those questions that were not already answered by the HDRS were directly asked/observed, in line with the authors recommended non-directive interview technique for the BPRS.

2.1.3 Cognitive Outcomes

2.1.3.1 The National Adult Reading Test

The National Adult Reading Test (NART-Appendix 8) (Nelson and Willison, 1991) was used as a measure of premorbid Intelligence Quotient (IQ) in depressed participants and current IQ in healthy controls. The NART contains 50 words with irregular spellings that the participant must try to correctly pronounce. The words vary in their frequency of usage, with those at the beginning of the test being more common and therefore more easily recognisable. Correct pronunciation of the irregular words implies previous knowledge of them, indicating a higher IQ. This test is also useful as vocabulary correlates highly with overall ability level and is relatively unaffected by most non-language related brain disorders (Lezak, 2004). Participants are shown cards with one word on each and are asked to try pronouncing the words shown.

Studies of reliability of the NART have shown high inter-rater reliability ($r = 0.96$- 0.98) and test-retest reliability ($r = 0.98$) (Crawford et al., 1989). The NART also shows high correlation levels ($r = 0.73$) in older non-demented adults with tests they had taken when aged 11, although a weak correlation with the Mini Mental State Examination (MMSE) ($r = 0.25$) was found for the same group (Crawford et al., 2001). Within a sample of the UK population the NART was found to correlate significantly with education ($r = 0.51$) and social class ($r = -0.36$) (Crawford, 1992), however a significant negative correlation with age ($r = -0.18$) did not account for any of the

variance in the sample (Crawford et al., 1988). No gender effects were found (Schlosser and Ivison, 1989).

2.1.3.2 The Addenbrooke's Cognitive Examination - Revised

The Addenbrooke's Cognitive Examination, revised, (ACE-R-Appendix 9) (Mioshi et al., 2006) was used as a measure of global cognitive function. The original Addenbrooke's Cognitive Examination (ACE) (Mathuranath et al., 2000) was developed to elaborate on the Mini Mental State Examination (Folstein et al., 1975) by expanding on memory, visuospatial and language components, with additional tests of verbal fluency, to assess key aspects of cognition (Mathuranath et al., 2000). The ACE contained six components that evaluated the following functions (with maximum scoring indicated); Orientation (10); Attention (8); Memory (35); Verbal fluency (14); Language (28); and Visuospatial ability (5). Raw scores were employed for all items except fluencies, which were scored on a scale instead.

The ACE was updated to increase its sensitivity and make it easier to administer, while content was modified to facilitate cross-cultural usage and translation (Mioshi et al., 2006). The number of categories was reduced from six to five and new sub-scores were constructed in each category, with new maximum scoring, as follows: Attention/orientation (18); memory (26); fluency (14); language (26); and visuospatial abilities (16). Within the fluency component the scaling of scores was revised so that a raw score of less than four on letter fluency could now be scored zero instead of one. Likewise, a raw score of less than five on category fluency now had a scaled score of zero instead of one. This had the overall effect of making fluency scoring more sensitive to lower scores. These changes resulted in increased sensitivity, whereby a score of 82 or lower was found to be 100 times more likely to be from a person with dementia than

a participant in the Mild Cognitive Impairment or control groups (Mioshi et al., 2006). The ACE-R also shows good reliability with a Cronbach's alpha coefficient of 0.80, and a significant, though moderate, correlation with the Clinical Dementia Rating instrument (Morris, 1997). The ACE-R has also been shown to differentiate between patients with cognitive impairment due to affective disorder and those with dementia (Dudas et al., 2005). Those with major depressive disorder were found to have mild impairment in the total ACE score, along with low scores on memory tasks and letter fluency.

2.1.3.3 Autobiographical Memory Interview Short-Form

The Columbia Autobiographical Memory Interview (AMI) (McElhiney et al., 1997, McElhiney et al., 1995) is used to assess consistency of autobiographical memory over time and retrograde amnesia following electroconvulsive therapy. To assess consistency of memories the instrument must be administered twice: at baseline to acquire details about specific memories and at a follow-up assessment to investigate recall performance of the original details. The AMI-SF (Appendix 10) is the shortened version of the original Columbia AMI (McElhiney et al, 1995) which itself is based on a personal memory questionnaire used in an earlier study (Weiner et al., 1986). The original AMI involved 281 inquiries about personal events, some of which examined events within the year prior to entering hospital while others examined more remote time periods. The full AMI took up to 210 minutes to administer.

The AMI-SF has been shortened to six categories, which involve five questions each, about a family member, most recent travel, last New Year's Eve, last birthday, most recent employment and last visit to a doctor for a physical complaint. At baseline interviewers encourage the participant to recall as much information as they can. Responses at baseline can be scored either two points for a recognisable real memory,

or zero for no memory or too little information to constitute a proper memory. Only those questions for which a memory had been retrieved at baseline were examined at follow-up. Follow-up assessments were scored as percentage recall of baseline score.

Although the AMI and AMI-SF have been widely used to examine autobiographical memory after ECT, the validity and reliability of these instruments has not been fully examined. However, it is discussed by McElhiney et al (1995) where the authors describe aspects of their findings which indicate that the AMI is a valid instrument for assessment of autobiographical memory. For example, at follow-up the participants are free to recall any memory on questioning, but are prompted to recall the original one when a different memory is recalled first. If the original still cannot be recalled after prompting, the authors conclude that this is evidence of memory impairment directly due to ECT. This can be taken to indicate that the AMI is suitable for capturing changes to autobiographical memory function from one time-point to another.

Secondly, a possible limitation of the AMI is that participants may recall the incorrect event at baseline and the correct event at follow-up. When this happens the correct event must be scored as an inconsistent memory, even though it is an improvement in memory, not a lapse of it. McElhiney et al (1995) investigated whether this situation might skew results. The authors compared consistency of recall between baseline and a later follow-up with consistency of recall between the post-treatment assessment and a later follow-up. No difference was found between the patterns of results for each comparison, indicating that incorrect memory recall at baseline was not a major influence on findings when using the AMI-SF (McElhiney et al, 1995).

There is a lack of normative data published for this instrument, and as such we have no way of knowing what scores qualify as being within the normal range of

forgetting and what qualifies as an impairment in autobiographical memory recall. The current research examines the AMI-SF in normal controls and in a depressed population who have never received ECT, in order to provide information regarding the effect of passage of time (baseline to follow-up) and depression itself on autobiographical memory. This information will provide a standpoint from which we can better understand the effect of ECT upon autobiographical memory.

Despite the limitations mentioned above, the AMI-SF remains the most commonly used instrument for assessment of autobiographical memory performance in patients treated with ECT. Gathering information about performance of normal controls and depressed participants on this instrument will ensure that findings from future research using the AMI-SF are correctly interpreted.

2.1.3.4 Public Events Questionnaire

The Public Events Questionnaire (Appendix 11) was based on previous similar questionnaires used in memory research (Howes and Katz, 1988, Warrington and Silberstein, 1970, Squire et al., 1989, Reed and Squire, 1998, Meeter et al., 2010) that contain questions about memorable events that have occurred over a number of years, from recent (i.e. within the last three years) to remote (i.e. prior to the last three years) time-periods.

Questions on public events memory tests are often grouped into a number of time-periods in order to assess the age of the memory, and participants are also often grouped by age in order to facilitate comparisons of chronological age. The current Public Events Questionnaire was developed for use with an Irish population, and questions were updated every six months. The Public Events Questionnaire assesses recent and remote memory for public events, spanning the 16 years prior to entering the

study. It is split into four time-periods, one which pertains to the most recent 12 months and three covering the 15 years before that, divided into three groups of five-year blocks. Categories covered include national news events, international news events and arts, sports and entertainment.

Questionnaires relating to public events memory have most often been studied with regard to participant demographics such as gender, age and media interest. In line with most studies in the social sciences, gender has frequently been studied with regard to its influence on public event memory questionnaire performance. Performance on political items, news events, sports (Howes and Katz, 1988) and business news (Meeter et al., 2010) has generally been shown to be higher for males than females, whereas women tend to perform better on entertainment and arts questions than other categories (Howes and Katz, 1988).

Age has been extensively studied within this area, which is not surprising given its central role in both the age of the memory being examined and the influence of chronological age on forgetting in general. With regard to age of the participant, studies have generally shown that older participants do not perform as well as younger participants on events that all have lived through (Howes and Katz, 1988, Squire and Slater, 1975, Bizzozero et al., 2004). In addition, younger participants, who were aged less than 12 years old at the time of the event being assessed, performed significantly worse than those who had been older than 12 at the time of the event (Howes and Katz, 1988). Age of the memory being studied (i.e. a recent versus a remote memory) has also been found to affect performance, although findings have varied across studies. Some authors have noted that while recent memory performance decreased with age, recall of remote memories remains at a constant level across time-periods (Howes and Katz,

1988, Squire and Slater, 1975). In contrast to this, others have shown more remote memories to be more susceptible to forgetting (Warrington and Sanders, 1971).

Finally, participants' interest in the media has been examined with regard to performance on public events questionnaires and has consistently been shown to be the most influential demographic characteristic on public events memory performance (Howes and Katz, 1988, Meeter et al., 2010).

One area that is relatively neglected in the assessment of public events memory is that of consistency of memory over time. Very few studies have looked at consistency and change in performance over time, where the same participants are tested on the same questionnaire on two occasions. One study looked at test-retest reliability after one month and found significant correlations between each time-point (Bizzozero et al., 2004). A second study (Squire et al., 1989) examined changes in performance over time and found that responses were consistent approximately 78% of the time for recall and 85% of the time for recognition. It is being increasingly recognised that control participants should be tested at all of the same time-points as experimental participants rather than just at baseline (McDermott, 2009) and in this case normative data for consistency over time on public events memory questionnaires needs to be more thoroughly investigated. Please refer to Chapter 3 for a comprehensive description and analysis of psychometric properties of the Public Events Questionnaire used for the current work presented in this thesis.

2.1.3.5 The Buschke Free and Cued Selective Reminding test

The Buschke Selective Reminding Test (BSRT) (Buschke and Fuld, 1974) was used to assess anterograde verbal learning and memory. In this study a common variant of the BSRT called the Free and Cued Selective Reminding (FCSR-Appendix 12) test

was used (Buschke, 1984). These tests are essentially a procedure for differentiating retention, storage and retrieval for verbal material, and can be administered in many different ways (Lezak, 2004). In the original BSRT participants usually hear or read a list of words which they must immediately recall, with most examiners using a list of 12 unrelated words. Over each subsequent recall trial only those words that were omitted in a previous trial are re-read/ re-shown to the participant. This system continues until all the words are recalled on two consecutive trials, or until the 12th trial (Lezak, 2004). When pre-defined criteria for immediate recall have been reached the participant will then proceed to a delayed recall trial, usually after 30 minutes or one hour.

In the FCSR variant of this test, 16 words belonging to 16 specific categories are presented to the subject. The categories are used to ensure semantic encoding takes place and to enhance retrieval. Participants are shown four words at a time, and asked which word belongs to a certain category. An immediate recall trial, with positive or negative feedback, occurs after every four words. If a word is not recalled the encoding task is repeated until the participant has recalled all of the words or until the test has to be stopped due to lack of encoding. An interference task is then employed, whereby the participant counts backwards from a given number, for a period of 20 seconds. On completing the interference task the participant is asked to recall all the words they can remember from the list, in one minute. Category cued recall follows this procedure and participants are asked for recall of only those words which they had missed during free recall. Following cued recall the same steps of interference, free recall and cued recall are repeated for two more trials. A recognition trial takes place at this stage. After a 20 minute delay a final free and cued recall trial is given.

One study compared the original selective reminding procedures with FCSR procedures, and found that in older adults twice as many words were consistently

recalled using FCSR as BSRT (Grober et al., 1997). The authors note that because this method ensures better attention and encoding, it provides a better estimate of the participant's best memory performance, which can then be used to determine whether memory impairment is present. With regard to validity, the FCSR procedure has been shown to predict dementia five years before diagnosis (Grober et al., 2000). In a study (n = 266) of demographic effects on performance on the FCSR, it was found that higher age, lower education and male gender were associated with lower recall scores (Grober, 1998). However, another study, in which most participants (n= 734) had no less than eight years education and those with preclinical dementia were not included, found that education did not influence scores on FCSR (Ivnik et al., 1997). Verbal memory, and BSRT performance, have been shown to be impaired in depression and, more specifically, depression may have a selective effect on encoding processes in verbal learning tests (Zakzanis et al., 1998).

In the current research three versions of the FCSR test were used for repeated testing. These versions were translated from a previous study in which words were matched across each parallel form for frequency, syllable length and semantic category. These parallel forms were then validated in 74 healthy participants (Van der Linden and GREMEM, 2004). However, the translated versions developed for this study were not tested for equivalence prior to use in the main research and therefore may not be equally difficult. This is a problem because test versions were not counterbalanced across participants, and as a result differences in performance over time may be due to non-equivalence of test version rather than a change in performance.

2.1.3.6 The Rey-Osterrieth Complex Figure Test

The Rey-Osterrieth Complex Figure (ROCF-Appendix 13) was used to investigate anterograde visual memory in depression. The original complex figure was developed by Rey (1941) to examine visual memory and perceptual organisation skills. It was standardised and normed and a scoring procedure developed for it by Osterrieth in 1944, hence it commonly being referred to as the Rey-Osterrieth Complex Figure (figure 4). A second figure was developed over 30 years later (Taylor, 1979) to provide an alternate figure for retesting, as were four further figures developed by researchers at the Medical College of Georgia (MCG; Loring et al, 2003).

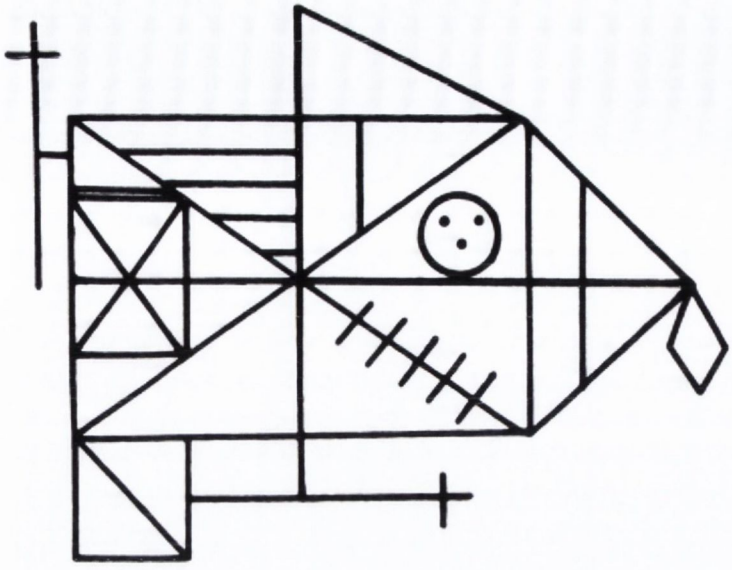


Figure 4: Rey-Osterrieth Complex Figure

There are three stages involved in complex figure testing: copy; immediate recall; and delayed recall. In the copy stage the participant is told that they will be shown a drawing that they must copy as well as they can. They are told they will be timed on this task but it is more important to copy the drawing correctly than quickly. In studies looking at perceptual ability examiners closely observe how the participants approach the copy task. When using the complex figure to examine memory function we are more interested in the immediate memory and delayed memory tasks. The immediate memory trial takes place after the copy task, often with a small delay of 30 seconds to three minutes. After the copy task, the examiner removes the original drawing from sight, places a sheet of paper in front of the participant and instructs them to draw the figure again from memory. If the participant thinks they made a mistake they are instructed not to erase it, but to correct it. After a 20 minute delay the same procedure is repeated for a final time. Each stage of the complex figure test is scored for how well each detail is originally copied and recalled, with reference to quality and correct spatial positioning of details. Training for the scoring of each figure was carried out under the guidance of a clinical and academic Neuropsychologist over three sessions, where initial scoring procedures were outlined, scoring was carried out under supervision and alone, and any differences in scoring were discussed and resolved.

Studies have found that scores on Taylor and MCG figures are generally comparable to each other, however, scores on the original Rey figure tend to be lower than those on the Taylor figure (Fastenau et al., 1999). This finding may have relevance for the current study in which versions of the complex figure were not counterbalanced across participants. Performance on immediate recall and delayed recall has been found to be similar when only one (either immediate or delayed) is administered; however, when both tasks are administered the delayed recall score tends to be higher than the

immediate recall score (Loring et al., 1990). Significant age effects are found with complex figure tests, with a decline in performance on immediate recall trials seen from the 40's onwards and delayed recall decline beginning in the 30's and progressing until the 70's (Lezak, 2004). A good level of education increases the age where decline is first seen, by approximately nine years (Boone et al., 1993). With regard to gender, men are found to perform better than women by some researchers (Rosselli and Ardila, 1991, Casey et al., 1991), although others have found no differences (Fastenau et al., 1999, Ingram et al., 1997). Inter-rater reliability has been shown to be high with values of r = 0.91 to 0.98 reported (Lezak, 2004). Test-retest reliabilities of alternate complex figures are slightly lower (r = 0.60 to 0.76) (Berry, 1991). Immediate and delayed recall scores have been found to have a strong visual memory component as well as strong visuospatial traits (Lezak, 2004).

2.1.3.7 Forward and Backward Digit Spans

Immediate short-term memory, attention and working memory were assessed using the Forward (Appendix 14) and Backward Digit Span (Appendix 15) procedures. This test is based on the Digit Span segment of the Wechsler Adult Intelligence Scale, revised (WAIS-R) (Wechsler, 1981). The version of the tests used here were taken from the test battery of the Core Assessment Program for Intracerebral Transplantation in Huntington's Disease (CAPIT-HD), with parallel forms developed for repeated testing of participants (Quinn et al., 1996). Both forward and backward digit span tests contain seven pairs of random number sequences, with two sequences of equal length in each pair. The examiner reads aloud at a rate of one number per second. Participants are instructed to listen carefully and, when the examiner has finished, repeat the numbers back. The same procedure is followed for digits backwards, except that participants are

given up to two practice trials to ensure they know what is expected of them. All number sequences should be read out until the participant fails to correctly recall both sequences of numbers in a set of two.

Digit span forward is thought to mainly measure efficiency of attention (Lezak, 2004). The normal range of span for digits forward is seven ± two (Miller, 1956). A span of five is seen as marginally normal, four as borderline and three as defective (Lezak, 2004). Age has been shown to have a minimal effect on digit span forward, from 65 to 70 years onwards (Craik, 1990, Jarvik, 1988), whereas education has a strong effect (Ardila and Rosselli, 1989, Kaufman et al., 1988). Test-retest reliability has been shown to range from moderate to strong ($r = 0.66$ to 0.89), depending on length of sequence and on age (Matarrazzo and Herman, 1984, Lezak, 2004).

Digit span backwards is a simple test of mental tracking and involves working memory. A backwards span of four to five is considered within normal limits; three is considered borderline and two as defective. Backwards span has been found to decrease by approximately one point during a participant's 60's and 70's. A factor analysis study found that digit span backwards is affected by both visual and verbal processes (Larrabee and Kane, 1986).

2.1.3.8 Trail Making Test Parts A and B

The trail making tests (TMT) were used to assess motor and psychomotor speed, divided attention and executive function in the current study. The tests were originally part of the Army Individual Test Battery (1944), but are now in the public domain and commonly used for neuropsychological testing. The tests used here were taken from the test battery of the CAPIT-HD, developed for repeated testing (Quinn et al., 1996). Part

A (Appendix 16) involves consecutively connecting numbers from 1 to 25 that are arranged randomly on a sheet of paper, as shown below (Figures 5 and 6).

Figure 5: Trail Making Test A

Figure 6: Trail Making Test B

Part B (above-Appendix 17) involves connecting randomly placed alternating numbers and letters in sequence. Test-takers are instructed to complete the tests "as fast as you can, without lifting your pen from the page". In this study we use the Reitan (1958) method of scoring the Trail Making Tests (Reitan, 1958). In this method errors are pointed out when they are made and the participant is allowed to fix them and proceed correctly. The main score is the time taken to correctly complete the trail.

The trail-making tests have been shown to have a motor component, with both motor speed and agility contributing to success of completing the trail (Lezak, 2004). Studies have also shown Part B to correlate with tests of mental flexibility, however, as similar types of correlations are also found to occur with Part A, the primary function of Part B cannot be described as testing mental flexibility (Kortte et al., 2002). Reliability of the Trail-making tests can vary but correlation coefficients are generally found to lie above $r = 0.60$ and in most cases are between $r = 0.80$ and $r = 0.90$ (Spreen and Strauss, 1998). Part A of the test shows practice effects, but scoring on Part B is usually too varied in the first place to show significant improvement (Lezak, 2004). Salthouse and colleagues found that visual searching skills, sequencing and motor speed components of the tests are affected by aging, but those involving executive function, or switching, are not (Salthouse et al., 2000). Education has also been shown to have an effect on test performance, especially for Part B, and women have been found to be slower at completing the test than men on Part B (Bornstein, 1985). One recent study has found that depressed participants take longer to complete the TMT than healthy controls (Gohier et al., 2009), although others report that levels of self-reported depression have minimal impact on TMT performance (Smitherman et al., 2007).

2.1.3.9 The Grooved Pegboard Test

The Grooved Pegboard Test (Appendix 18 (Klove, 1963)) was used to assess fine eye-hand coordination, lateralised impairment and psychomotor speed. The Grooved Pegboard is made up of five rows and five columns of slotted holes, as shown below (Figure 7).

Figure 7: The Grooved Pegboard

Each peg is rounded on one side, with a rectangular groove jutting out on the other side. The pegs must be slotted into each hole in the appropriate orientation, as fast as possible. The score is the time taken to insert all 25 pegs correctly into the board.

Age has been found to be associated with a decrease in speed of performance on the Grooved Pegboard, whereas education has been shown to affect the dominant hand only (Bornstein, 1985), or have no effect at all (Heaton et al., 1996). With regard to gender differences, small but significant differences were found using the dominant hand, whereby men were slower than women at completing the pegboard (Schmidt et al., 2000, Bornstein, 1985) and these differences were found to be smaller again using the non-dominant hand (Ruff and Parker, 1993). Test-retest reliability has been found to be good ($r \geq 0.82$) for the Grooved Pegboard. With regard to validity, studies have noted that it is a useful instrument for measuring general slowing due to medication (Lewis and Rennick, 1979, Matthews and Harley, 1975). Recent studies have reported that there are some data to suggest that psychomotor speed is sensitive to clinical state in a younger depressed population and in adults, which shows improvement with successful treatment for depression (Douglas, 2009).

2.1.4 Electroconvulsive therapy

Electroconvulsive therapy was administered with hand-held electrodes according to Royal College of Psychiatrists' guidelines (Royal College of Psychiatrists, 2005) in a manner reported in previous studies (Eranti et al, 2007). A Mecta spECTrum 5000m ECT Device was used to deliver brief pulse stimulation. Seizure duration was measured by Electro encephalogram (EEG) monitoring. Methohexitone (0.75-1.0 mg/kg) was used for anaesthesia with suxamethonium (0.5-1.0 mg/kg) as muscle relaxant. The current was passed between the two hand-held electrodes, which were

placed either bilaterally (BT) (bitemporal position) or unilaterally (UL) on the right side of the brain (d'Elia position). Seizure threshold (ST), the minimum electrical charge needed to induce a generalized seizure lasting at least 25 seconds, was established at the first session and subsequent treatments were given at 1.5 times ST for BL ECT and 6.0 times ST for RUL ECT.

2.2 Methods

This research consisted of two separate but parallel studies, the Mem-Dep study and the EFFECT-Dep trial. Methods for each study are outlined here.

2.2.1 Project 1: Mem-Dep study - A Study of Retrospective Memory in Depression

2.2.2.1 Ethics and Consent

Full ethical approval was granted for this study by the St. Patrick's University Hospital Research Ethics Committee (Protocol number 01/08-Appendix 19) and the Trinity College Dublin, School of Medicine, Faculty of Health Sciences Research Ethics Committee (Appendix 20).

The main entry criterion to the study was referral for treatment of a major depressive episode. Potential study participants were identified following referral and admission to St. Patrick's University Hospital and St. Edmundsbury Hospital, Dublin. Patients were provided with both written and oral information (Appendix 21) and given at least 24 hours to consider their participation. Any additional questions or concerns of the participant were addressed by the researcher prior to commencing the study. Written consent was provided by each participant (Appendix 22). Participation was on a

voluntary basis and participants were informed that they were free to withdraw from the study at any time.

2.2.2.2 Design

This study was a between group case-control study with a repeated measures design. The independent variables were Time (with four levels for patients: baseline, two, six and 12 months; and three levels for controls: baseline, six and 12 month) and group (with two levels: depressed and control). The two main dependent variables were: retrospective memory function and depression severity. Retrospective memory function was measured by the AMI-SF (McElhiney et al., 1995, McElhiney et al., 1997) which measures autobiographical memory and a Public Events Questionnaire, which measures long-term memories for public events and was generated specifically for this study. The second dependent variable was severity of depression, measured in both depressed participants and healthy controls using the HDRS-24 (Hamilton, 1960, Kovacs et al., 1981). This study took place under real-world conditions and all depressed participants remained on medication as prescribed by their treating consultant. Current medication was recorded at each assessment point.

Analyses of the study focused on three main sections: investigation of psychometric properties of the Public Events Questionnaire in healthy controls; comparison of retrospective memory function in depressed participants during a major depressive episode with that of healthy controls (i.e. at baseline); and investigation of retrospective memory function over a 12 month follow-up period in depressed participants and healthy controls.

The main assessment outcomes of interest in the current study were the retrospective memory questionnaires (AMI-SF and Public Events Questionnaire). These

measures had not previously been used in a depressed population, and as such when determining sample size previous publications were not available to carry out a power calculation. Instead, previous similar studies were considered and it was aimed to recruit a similar number of participants. In the current study at least 30 depressed and 30 control participants were sought.

2.2.2.3 Depressed participants

Each new in-patient admission was considered for the study and possible candidates were identified according a clinical diagnosis of depressive disorder on admission. With the approval of the referring physician, a research worker directly approached potential participants to outline the study objectives and discuss their possible involvement. Informed consenting patients were invited to participate in the study.

Patients ≥18 years admitted to St. Patrick's University Hospital or St. Edmundsbury Hospital with unipolar major depressive disorder (diagnosis confirmed using SCID-1, DSM-IV criteria (American Psychiatric Association, 2000, First et al., 1995)) and a HDRS-24 score of ≥ 21, were invited to participate. Participants could not have a co-morbid psychiatric diagnosis, except where anxiety was diagnosed secondary to major depressive disorder. All participants required English as their first language.

Exclusion criteria comprised diagnosis of dementia or other Axis 1 diagnosis; alcohol/other substance abuse in previous six months; past history of treatment with ECT; major sensory deficit; inability/refusal to consent.

2.2.2.4 Control Group

Healthy control participants were recruited through advertisements in local businesses, social and sports clubs and from online volunteer and community websites. Controls were also recruited from the student population in Trinity College Dublin. Controls were recruited into the study consecutively. Participants contacted the researcher directly by telephone or email. The researcher provided all possible participants with written information about the study and screened participants with a short questionnaire to ascertain whether they met inclusion and exclusion criteria for the study.

All controls were aged $\geq$ 18; had English as first language; had a HDRS-24 score of $\leq$8 and MMSE $\geq$26 (Folstein et al., 1975). Controls were excluded from participation if they had any past psychiatric history; previous ECT; current major medical illness/major sensory deficit; alcohol/other substance abuse in previous six months; or inability/refusal to consent.

Based on finding of previous studies it was estimated that 69 patients would be required per treatment group to have 80% power to demonstrate a mean reduction in HDRS-24 score is no more than 4 points less than that achieved using standard BT ECT (Petrides et al., 2001) and to detect differences between the two ECT groups of at least 4.5 points in AMI-SF scores at end-of-treatment (Sackeim et al., 2007).

2.2.2.5 Procedure

Once consenting participants met relevant inclusion and exclusion criteria the neuropsychological testing was carried out. The complete assessment battery was carried out at all assessments where possible. Baseline assessment of depressed participants was carried out as soon as suitable participants were identified following

admission. Depressed participants were followed up at two, six and 12 months after the initial assessment, as outlined below. Control participants were assessed at baseline, six and 12 months. Standardised neuropsychological and clinical assessments were used where possible and many tests were chosen for comparability to those used in other similar published studies. Parallel versions of assessments were used where possible. However, parallel versions were not counterbalanced across participants. This may have been an issue when using the Buschke FCSR (see section 2.1.3.5) and the Rey-Osterrieth Complex Figure (see section 2.1.3.6), and is noted where applicable in discussions of findings. The complete assessment battery, in order of administration, is shown in Table 1. Training in administration of assessments was carried out by a Psychiatrist and Clinical Neuropsychologist.

Assessment	baseline		2 month follow-up		6 month follow-up		12 month follow-up	
	Patient	Control	Patient	Control	Patient	Control	Patient	Control
HDRS[24]	✓	✓	✓		✓	✓	✓	✓
SCID-I	✓	✓						
Treatment Review	✓	✓	✓		✓	✓	✓	✓
ATHF	✓							
NART	✓	✓						
BPRS	✓	✓	✓		✓	✓	✓	✓
AMI-SF	✓	✓	✓		✓	✓	✓	✓
Public Events Questionnaire	✓	✓	✓		✓	✓	✓	✓
ACE-R	A	A	B		C	B	D	C
Digit span	I	I	II		III	II	I	III
Buschke FCSR	1	1	2		3	2	1	3
ROCF	A	A	B		C	B	D	C
Trail Making Test	✓	✓	✓		✓	✓	✓	✓
Grooved Pegboard Test	✓	✓	✓		✓	✓	✓	✓
BDI-II	✓	✓	✓		✓	✓	✓	✓

Table 1: Schedule and list of Mem-Dep assessments

ATHF: Antidepressant Treatment History Form; SCID-I: Structured Clinical Interview DSM-IV, Axis 1; HDRS-24: Hamilton Depression Rating Scale; NART: National Adult Reading Test; ACE-R: Addenbrooke's Cognitive Examination, revised (Parallel versions A,B,C,D); AMI-SF: Autobiographical Memory Interview, Short-form; Buschke Free and Cued Selective Reminding (FCSR) with parallel versions 1, 2 and 3; ROCF: Rey-Osterrieth Complex Figure with parallel versions A, B, C, D; Digit Span (Forwards and Backwards) with parallel versions I, II and III; TMT-A: Trail Making Test Part A; and TMT-B: Trail Making Test Part B.

Participants with a history of dyslexia were not tested on the NART due to difficulty in reading irregular words. The ACE-R was used to provide a measure of global cognitive function, a MMSE score, and letter and category fluency performance. The digit span tests were carried out prior to any tests that involved delayed recall to avoid unwanted interference effects during the delay period.

The Buschke FCSR test and the Rey-Osterrieth Complex Figure Test (ROCF) both involved 20 minute delay periods before delayed recall. The Buschke FCSR was performed first. During the delay phase the copy and immediate recall tasks of the ROCF were carried out, followed by the Trail Making Test, and the Grooved Pegboard test. As such, the Trail Making Test, Grooved Pegboard test and the delayed recall section of the Buschke FCSR test were carried out during the ROCF delay period.

In cases where participants were hospitalised at the time of baseline or follow-up assessment, testing sessions were often conducted over two or three separate occasions, to ensure the wellbeing of participants who found testing difficult. Outside of this situation, testing took approximately two hours to complete. Participants were encouraged to complete all assessments where possible. The researcher was present at all times and guided participants through all assessments. Participants in the depressed group were tested at an extra time-point of two months after initial testing. This time-point represented the average length of stay in the hospital, and allowed for assessment of differences in cognitive functioning from the beginning of the hospital stay to two months later.

Participants were contacted by telephone and/or email to arrange follow-up testing sessions, approximately one month prior to testing to arrange appointments. Where participants were unable to travel to the hospital for testing the researcher was available to go to the individual's home instead. If this was not agreeable to the

participant assessments were carried out by telephone. Where this occurred, the HDRS-24, AMI-SF and Public Events Questionnaire were prioritised, followed by any other assessments that could be done by telephone (Fluencies from the ACE-R, Digit span, BPRS). High correlations in test-retest reliability have previously been reported for HDRS interviews carried out by telephone (Potts et al., 1990).

2.2.2 Project 2: EFFECT-Dep Trial- Enhancing the effectiveness of electroconvulsive therapy in severe depression

Bilateral (BL) ECT has been shown to be an effective treatment for severe depression (UK ECT Review Group, 2003). However, impairment in memory is often reported as a side-effect of BL ECT (Lisanby et al., 2000). In comparison, less cognitive side-effects are reported after unilateral (UL) ECT. Standard dose UL ECT has been shown in the past to be less effective than BL ECT. However, more recent research suggests high-dose UL ECT is as efficacious as BL ECT, and may produce fewer cognitive side-effects (Sackeim et al., 2000, Kellner et al., 2010a). The EFFECT-Dep randomized controlled trial (RCT) investigates both the efficacy and side-effect profile of standard BL ECT and high dose right UL ECT. The study is a two-group parallel-design randomised controlled non-inferiority trial. The trial is registered with Current Controlled Trials Ltd., trial number: ISRCTN23577151. Consented patients with major depressive disorder (SCID-I, DSM-IV) are randomly allocated to a course of BL ECT (1.5 x seizure threshold - ST) or high-dose right unilateral (RUL) ECT (6.0 x ST). Participants were tested on clinical and neuropsychological assessments before starting ECT treatment and for up to 12 months after finishing ECT treatment. To facilitate generalisabilty of results, the trial takes place under "real world" conditions and so both groups continue usual care and medications during treatment phase and thereafter.

In the current study the focus is on a sub-section of data collected as part of the EFFECT-Dep Trial. In particular, the focus of the present study was to examine the effect of ECT subtype (BL or UL) on retrospective memory by comparing pre-ECT and post-ECT performance on neuropsychological tests. Recovery of function over time was also examined at three month and six month follow-up.

2.2.2.6 Ethics and Consent

Full ethical approval was granted for this study by the St. Patrick's University Hospital Research Ethics Committee (Protocol number 012/07-Appendix 23) and the St. James's Hospital/Adelaide Meath & National Children's Hospital Research Ethics Committee (Protocol number 2008/05/04-Appendix 24). All participants were given verbal and full written information (Appendix 25) and asked to provide written informed consent (Appendix 26).

2.2.2.7 Randomisation and Blinding

Patients were randomised after baseline data collection. Patients and assessors were blind to treatment; clinicians administering ECT were not involved in assessments or data analysis. Success of blinding for patients and raters was assessed after the second and final ECT treatment. Simple random allocation was done independently by the Clinical Trials Unit at the Institute of Psychiatry (IOP, London) to ensure allocation concealment. Randomisation incorporated minimisation strategies to account for the following issues, and ensure they were spread evenly across groups with each new participant:

1: Previous ECT- whether the patient has had ECT before or not

2: Site- the source of the referral:

i. St. Patrick's University Hospital or St. Edmundsbury Hospital

ii. St. James's Hospital

iii. Other public (Health Service Executive) hospital

2.2.2.8 Participants

The main entry criterion to the study was being referred for ECT for treatment of a major depressive episode. With the approval of the referring physician, a research worker directly approached potential participants to outline the objectives of the study and discuss their involvement. If eligible and able to consent then the patients were invited to participate in the study.

Patients ≥18 years with major depressive disorder (meeting SCID-I criteria) and referred for ECT were invited to participate. Exclusion criteria included: any condition in which patients were deemed medically unfit for general anaesthesia or ECT; treatment with ECT in previous six months; dementia or other Axis 1 diagnosis; alcohol/other substance abuse in previous six months; inability/refusal to consent.

2.2.2.9 Interventions

ECT was administered twice weekly with hand-held electrodes according to Royal College of Psychiatrists' guidelines (Royal College of Psychiatrists, 2005). Seizure duration was measured by EEG monitoring. Methohexitone (0.75-1.0 mg/kg) was used for anaesthesia with suxamethonium (0.5-1.0 mg/kg) as muscle relaxant. Seizure threshold (ST) was established at the first session and subsequent treatments were given at 1.5 times ST for BL ECT and 6.0 times ST for RUL ECT. Stimulus charge was titrated upwards as required during treatment courses following a standard stimulus dosing protocol (Royal College of Psychiatrists, 2005). To reflect routine

clinical practice, number of ECT treatments was determined by referring physicians who were blind to randomisation.

2.2.2.10 Procedure

All patients who were prescribed ECT treatment in St. Patrick's and St. Edmundsbury Hospitals were considered for entry to the EFFECT-Dep trial. Once a patient met criteria and agreed to enter the trial the baseline assessments were conducted. Any baseline assessments completed had to be carried out prior to the participant undergoing their first ECT treatment. Due to the nature of depressive illness, some participants were unable to complete all assessments at baseline. In such cases, the minimum requirement to enter the study was a completed SCID and HDRS-24. During ECT treatment, trial participants were assessed on the HDRS-24 after every two treatments received. This "intra-treatment" assessment was used as a measure of response to treatment. The full assessment battery (see Table 2) was again carried out at End of Treatment (EOT-last treatment in the course, or after the 12^{th} treatment if receiving more than 12 treatments), three month and six month follow-up. All assessments were carried out as described in the Mem-Dep study procedure. In line with the Mem-Dep study, in the EFFECT-Dep group the assessments were used to examine baseline (pre-ECT) cognitive function in severe depression. An EOT follow-up allowed for examination of any changes to cognitive function after undergoing ECT. Follow-up assessments at three and six months after EOT were carried out to investigate longitudinal change or recovery of cognitive function after ECT, and examine any differences in performance between high-dose RUL ECT and standard BL ECT.

	Baseline	End of treatment	3 month follow-up	6 month follow-up
HDRS[24]	✓	✓	✓	✓
SCID-I	✓			
Treatment Review	✓	✓	✓	✓
ATHF	✓			
NART	✓			
BPRS	✓	✓	✓	✓
AMI-SF	✓	✓	✓	✓
Public Events Questionnaire	✓	✓	✓	✓
ACE-R	**A**	**B**	**C**	**D**
Digit span	**I**	**II**	**III**	**I**
Buschke FCSR	**1**	**2**	**3**	**1**
ROCF	**A**	**B**	**C**	**D**
Trail Making Test	✓	✓	✓	✓
Grooved Pegboard Test	✓	✓	✓	✓
BDI-II	✓	✓	✓	✓

Table 2: Schedule and list of EFFECT-Dep assessments

ATHF: Antidepressant Treatment History Form; SCID-I: Structured Clinical Interview DSM-IV, Axis 1; HDRS-24: Hamilton Depression Rating Scale; NART: National Adult Reading Test; ACE-R: Addenbrooke's Cognitive Examination, revised (Parallel versions A,B,C,D); AMI-SF: Autobiographical Memory Interview, Short-form; Buschke Free and Cued Selective Reminding (FCSR) with parallel versions 1, 2 and 3; ROCF: Rey-Osterrieth Complex Figure with parallel versions A, B, C, D; Digit Span (Forwards and Backwards) with parallel versions I, II and III; TMT-A: Trail Making Test Part A; and TMT-B: Trail Making Test Part B.

2.2.3 Quality Control

2.2.3.1 Inter-rater reliability

Inter-rater reliability was assessed in the current research, for both overall and individual item reliability on the HDRS-24, prior to recruiting participants. Each rater was recorded conducting a HDRS-24 interview, with a minimum of five depressed inpatients in St. Patrick's University Hospital. These patients had consented to be filmed for educational purposes and were not participants in either study. Recorded interviews were watched and rated by every researcher who administered the HDRS-24 as part of the Mem-Dep and EFFECT-Dep studies. Original inter-rater reliability was found to be high for total scores on the HDRS-24 but reliability was found to be weak for a few individual items. Rating of the problematic items was discussed and strict guidelines were developed for these questions. Inter-rater reliability assessments were subsequently carried out every six months to ensure that reliability remained high across the course of each study. Over the course of 3 years, reliability scores ranged from 0.85 to 0.97 (ICC) for the EFFECT-Dep study and 0.93 to 0.97 (ICC) for the Mem-Dep study, indicating that a very high level of inter-rater reliability on the HDRS-24 was achieved and maintained for each study.

2.2.3.1 Data Quality

A quality control procedure was in place for organising data from both studies. The process had five levels of data checking for each completed assessment. These checks identified any mathematical and/or transcription errors in the calculation and entering of the data. The levels are:

1. Each team member corrected assessments they had carried out.
2. Each team member was paired with another team member. Once a fortnight this pair cross checked each other's first level ratings for errors.
3. Every two weeks the team leader ensured all checks were complete and correct and every four weeks a team discussion regarding any problems remaining unresolved was held.
4. Monthly data entry into SPSS Data Entry Builder programme.
5. Every six months statistical analyses were carried out to uncover any input errors.

2.3 Data Analyses

All analyses of data was carried out using SPSS version 16 (SPSS Inc., 2009). Results are presented as mean (M) and standard deviation (SD). Correlational analyses, t-tests and mixed between-within measures analyses of variance (ANOVAs) were conducted (see individual results chapters for more details). Where data was not normally distributed non-parametric equivalent analyses were conducted instead.

CHAPTER 3: PSYCHOMETRIC PROPERTIES OF THE PUBLIC EVENTS QUESTIONNIARE

INTRODUCTION

Public events questionnaires (Howes and Katz, 1988, Meeter et al., 2010, Reed and Squire, 1998, Squire et al., 1989, Warrington and Silberstein, 1970) contain questions about memorable events that have occurred over a number of years, often grouped into distinct time-periods. Studies have shown older participants and those under 12 years old perform worse than others on these questionnaires (Bizzozero et al., 2004, Howes and Katz, 1988, Squire, 1975). Gender has been found to affect performance on different categories (Howes and Katz, 1988, Meeter et al., 2010), as has interest in media (Meeter et al., 2010). Findings regarding better preservation of older memories have been mixed (Howes and Katz, 1988, Squire and Slater, 1975, Warrington and Sanders, 1971).

Consistency of memory over repeated assessments has rarely been studied, but the few studies that have addressed this have reported high levels of consistency from one time-point to another (Bizzozero et al., 2004, Squire et al., 1989), however this issue was not the primary concern of these particular studies, and participant numbers were very low (n=8-15). A measure of how much memory is lost from one time period to another is often useful in clinical situations and as such we need to know how consistent recall is in a normal population. Public events questionnaires may be used in this way to demonstrate how much information known at baseline is retained at follow-up.

An important consideration when using public events questionnaires is that a new test generally has to be developed for each research team that uses it, in order to ensure questions are up to date and tailored for use with the population of the country or culture that the research sample is taken from. Another issue inherent in the development of public events questionnaires is the need for regular updating of questions. This becomes especially important in longitudinal studies, such as clinical trials, where participants may be recruited over several years. In this situation, it is necessary to ensure that test items are from equally distant periods of time for all participants. Some authors have looked at methods of updating public events questionnaires (Bizzozero et al., 2004) but to my knowledge no studies have been reported on comparing performance between original and updated versions of a Public Events Questionnaire. Taken together, these issues highlight the need to develop a method of constructing and easily updating public events questionnaires to ensure that findings are comparable across studies.

Therefore, this chapter examines the construction of a Public Events Questionnaire that can be easily tailored to specific populations and easily updated for use with a sample that is recruited over a long time-period. Consistency of performance on two occasions was investigated for three updated versions of the Public Events Questionnaire. Secondary exploratory analyses were also carried out to examine validity of the public events questionnaire.

3.1 Methods

3.1.1 Participants

This study sought to assess consistency for public events memory in healthy non-depressed persons and the feasibility of updating a PEQ for a study where recruitment may take place over a long time. All participants were ≥ 18 years, had English as first language, scored ≤8 on the Hamilton Rating Scale for Depression (HRSD) (Guy, 1976) and had Mini Mental State Examination (MMSE) (Folstein et al., 1975) scores of ≥26. Participants had no previous psychiatric history, no cognitive impairment, no current major medical illness/major sensory deficit and no alcohol/other substance abuse in the previous six months. Full informed written consent was obtained from participants prior to commencing the study and full ethical approval was granted for this study by the St. Patrick's University Hospital Research Ethics Committee (Protocol number 01/08) and the Trinity College Dublin, School of Medicine, Faculty of Health Sciences Research Ethics Committee. Volunteers were recruited through advertisements in local businesses; online volunteering websites; social and sports clubs; and Trinity College Dublin.

3.1.2 Materials

All volunteers completed a cognitive test battery which included measures of current IQ (National Adult Reading Test, NART (Nelson and Willison, 1991)), global cognitive functioning (Addenbrooke's Cognitive Examination, Revised, ACE-R (Mioshi et al., 2006) incorporating Mini Mental State Examination (MMSE) and semantic and phonological fluencies), and the Public Events Questionnaire designed for this study. In addition participants completed the Rey-Osterrieth Complex Figure (ROCF)(Osterrieth, 1944, Taylor, 1979) as a measure of anterograde visual learning and

delayed memory and the Buschke Free and Cued Selective Reminding Test (FCSR) (Buschke and Fuld, 1974) as a measure of anterograde verbal learning and delayed memory.

3.1.3 Public Events Questionnaire

The Public Events Questionnaire was based on previous similar questionnaires (Howes and Katz, 1988, Meeter et al., 2010, Reed and Squire, 1998, Squire et al., 1989, Warrington and Silberstein, 1970) used in memory research. It was updated and tailored for use with an Irish population.

3.1.3.1 Design of the Public Events Questionnaire

Three versions of the Public Events Questionnaire (Version 3-Figure 8, See Appendix 11 for all versions) have been used in this study. The versions were updated every six months with new revised versions starting on the first day of January and July respectively. Updating the questionnaire every 6 months ensures that the most recent questions are never more than 12 months old at the time of initial testing. This is an important consideration for studies that recruit participants over a long period of time (e.g. clinical populations). Participants were always tested on the same version of the questionnaire at each testing session.

The questionnaire spans the 16 years prior to entering the study. It is split into four time-periods, one which pertains to the most recent 12 months (Events Questionnaire time-period 1- EQ1) and three covering the 15 years before that, divided into three groups of five-year blocks (EQ5, EQ10 & EQ15). EQ5 contains questions from the 5 year period immediately preceding the most recent 12 months (2-6 years ago inclusive), EQ10 contains questions from the 5 years before that (7-11 years ago

inclusive) and EQ15 contains questions from the five year period before that again (12-16 years ago inclusive).

Each time-period is made up of 15 questions covering three public events categories:

1- National news events

2- International news events

3- Cultural events (including arts, sports and entertainment)

This results in a total of 60 items for the entire questionnaire. The first version of the questionnaire contained 9 national questions, 23 international questions and 28 cultural questions. Although other similar questionnaires also contain an uneven number of questions in each category (Warrington and Silberstein, 1970) the Public Events Questionnaire was modified to 20 questions per category for Versions 2 and 3 in order to ensure a more even spread of categories across each time period and to enable ease of updating of the questionnaire. As such, Versions 2 and 3 contain 5 questions on each category in each time-period, one of each category per year. Questions from all time-periods and categories were randomly distributed across the questionnaire when it was administered.

VERSION 3	Jul93-Jun98	Jul98-Jun03	Jul03-Jun08	Jul08-Jun 09
1) Name the Cambodian Khmer Rouge leader who died in 1998, whose attempts to form a Communist society resulted in the deaths of 25 percent of the country's population? Ho Chi Minh, General Mao, **Pol Pot,** Idi Amin		□		
2) Who was the British journalist and presenter of the BBC program *Crimewatch* who was shot dead on the doorstep of her home in April 1999? **Jill Dando,** Anne Diamond, Fiona Bruce, Kay Burley		□		
3) What was the name of the controversial Irish swimmer who won 3 gold medals in the 1996 Olympics? Natalie Coughlin, **Michelle Smith**, Jenny Thompson, Lynn Joyce	□			
4) Which two South African politicians won the Nobel Peace prize in 1993 for working towards Democracy and an end to Apartheid? Steve Biko & Nelson Mandela. **Nelson Mandela & FW De Clerk**, Nelson Mandela & Winnie Mandela, Steve Biko & Winnie Mandela	□			
5) Senior citizens marched in protest in Dublin in November 2008 after the removal of what benefit in the budget? Free travel, Fuel allowance, Childrens allowance, **Medical cards**				□
6) Which animals were at the centre of a food contamination scare in Ireland in late 2008? Lambs, **pigs,** cattle, poultry				□
7) Which member of the Beatles died in 2001 aged 58? Paul McCartney, **George Harrison,** John Lennon, Ringo Starr		□		
8) Which Irish politician was appointed UN High Commissioner for human rights in 1997? **Mary Robinson,** Mary McAleese, Adi Roche, Mary Harney	□			
9) Which Irish golfer won the British Open championship and the USPGA tour in 2008? Darren Clarke, **Padraig Harrington,** Paul McGinley, Christy O'Connor				□

	Jul93-Jun98	Jul98-Jun03	Jul03-Jun08	Jul08-Jun 09
10) Who did Enda Kenny replace as leader of Fine Gael in 2002? John Bruton, Jim Mitchell, **Michael Noonan**, Garrett Fitgerald		□		
11) Which now famous Dublin structure on O'Connell Street was completed in 2003? Nelson's Column, **The (Millenium) Spire (of Dublin)**, Croke Park, Landsdowne Road		□		
12) In which country were the FIFA world cup soccer finals held in 2006? England, France, **Germany**, Holland			□	
13) Who was sworn in as President of Afghanistan in 2001? Ruhollah Khomeini, Saddam Hussein, **Hamid Karzai,** Ahmed Shah Massoud		□		
14) What nationwide ban came into effect in public places in March 2004? Hunting ban, **Smoking ban,** shooting ban, drinking ban			□	
15) Which Indian city was the site of terrorist attacks on tourists in November 2008? Delhi, Calcutta, **Mumbai,** Goa				□
16) What was the name of the Alaskan politician who ran for vice-president in the 2008 American presidential elections? **Sarah Palin**, Condoleeza Rice, John Kerry, John McCain				□
17) Which controversial former Taoiseach, known for his extravagant lifestyle, died in 2006? **Charlie Haughey,** Albert Reynolds, John Bruton, Garret Fitzgerald			□	
18) In a controversial decision Aer Lingus decided to cease direct flights between Heathrow airport and which Irish airport in 2008? **Shannon,** Knock, Cork, Galway				□
19) What was the name of the Treaty that was rejected in Ireland in June 2008? **The Lisbon Treaty**, The Nice Treaty, The Maastricht Treaty, The Madrid Treaty			□	

	Jul93-Jun98	Jul98-Jun03	Jul03-Jun08	Jul08-Jun 09
20) Which former Taoiseach, originally from County Cork, died in October 1999? Charlie Haughey, Seán Lemass, Liam Cosgrave, **Jack Lynch**		□		
21) Who became 44th President of the United States on January 20th 2009? Joe Biden, John McCain, Hilary Clinton, **Barack Obama**				□
22) Which American swimmer won 8 gold medals in the 2008 Olympic games? Ian Thorpe, Mark Spitz, **Michael Phelps,** Barry Murphy				□
23) Which actor in 1995 was seriously injured during a riding accident and left wheelchair – bound? Billy Crystal, **Christopher Reeve**, Adam Sandler, Alan Watts	□			
24) What was the name of the world's first successfully cloned mammal? Percy the pig, Harry the horse, **Dolly the sheep,** Daisy the cow	□			
25) Which county won the all Ireland football final in 2008? Kerry, Cork, **Tyrone,** Armagh				□
26) In 1995, which Bosnian town was the site of a massacre of men and boys during the Yugoslav war? Mostar, Belgrade, Krajina, **Srebernica**	□			
27) What animal disease outbreak in 2001 caused the closure of public parks and gardens, the cancellation of the St. Patrick's day parade and the culling of thousands of animals in Ireland and the UK? Bird Flu, Bluetongue, **Foot and mouth,** Mad cow disease		□		
28) Which Irish actor won a Golden Globe in January 2009 for his performance in the film "In Bruges"? Gabriel Byrne, Liam Neeson, **Colin Farrell,** Daniel Day-Lewis				□
29) Which natural disaster took place in South East Asia on the 26th of December 2004? Volcanic Eruption, Hurricane, Landslide, **Tsunami**			□	

	Jul93-Jun98	Jul98-Jun03	Jul03-Jun08	Jul08-Jun 09
30) Which world famous American popstar, famous for hits like "Thriller" and "Billy-Jean" died in June 2009? Frank Sinatra, Justin Timberlake, **Michael Jackson,** Bruce Springsteen				□
31) Which city in Louisiana, USA was severely affected by Hurricane Katrina in 2005? **New Orleans**, Baton Rouge, Detroit, New Haven			□	
32) Which former actor was elected as governor of California in 2003? Ronald Reagan, Harrison Ford, **Arnold Schwarzenegger**, Ted Dansen			□	
33) On November 24, 1995, the Irish population voted to remove Ireland's constitutional ban on what issue? Abortion, Smoking, **Divorce,** Euthanasia	□			
34) Which British actress starred in the film "Titanic" in 1997? Kate Beckinsale, Keira Knightley, **Kate Winslet,** Helen Mirren	□			
35) Which famous female tennis player was stabbed on court in 1993? Martina Hingis, **Monica Seles**, Martina Navratilova, Jennifer Capriati	□			
36) Which famous Irish singer from Mullingar died on the 26th of December 2007? Dana, **Joe Dolan**, Paddy Reilly, Luke Kelly			□	
37) Which American figure skater was attacked by fellow skater Tonya Harding's ex-husband prior to the 1994 Winter Olympics, in a bid to remove her from the American Olympic team? Jane Torville, **Nancy Kerrigan,** Sarah Coen, Michelle Kwan	□			
38) Which party entered coalition government with Fianna Fail for the first time in 2007? The Progressive democrats, The Labour Party, **The Green Party,** the Workers Party			□	
39) Which former president of Serbia was found dead in his cell in The Hague in 2006? Radovan Karidic, General Tito, **Slobodan Milosevic**, Ratko Mladic			□	

	Jul93-Jun98	Jul98-Jun03	Jul03-Jun08	Jul08-Jun 09
40) Which team beat Galway to win the All Ireland Senior Hurling Championship in 2005? **Cork**, Kilkenny, Tipperary , Limerick			□	
41) What was the name of the Russian Submarine that sank in 2000 in the Berints Sea with the loss of all crew? The October, The Pyotr Velikiy, The Komsomolets, **The Kursk**		□		
42) What new influenza virus spread from Mexico throughout the world in April 2009? **Swine flu,** Avian flu, Spanish flu, Hawaiian flu				□
43) Which Asian country came under international scrutiny in May 2009 after carrying out tests of nuclear weapons? South Korea, China, **North Korea,** Japan				□
44) Which former Pakistani Prime Minister was assassinated on December 27th 2007? Nawaz Sharif, **Benazir Bhutto**, Indira Gandhi, Tarviz Musharaf			□	
45) Which Fianna fáil TD was sentenced to 6 months imprisonment for tax offences in 2005 as a result of legislation he had passed? Bertie Ahern, Charlie Haughey, **Ray Burke,** Tony O'Reilly			□	
46) What was the name of the Irish Crime Reporter who was shot dead in Dublin in 1996? Emily O'Reilly, **Veronica Guerin**, Yvonne Fletcher, Veronica Lake	□			
47) Which former American Football star was arrested in 1994 for the murder of his ex-wife Nicole and her friend Ron Goldman? **OJ Simpson**, Joe Montana, Bruce Smyth, Bill Giles	□			
48) Who was promoted to chief executive of low-cost airline Ryanair in 1994? David O'Leary, **Michael O'Leary**, Dermot Mannion, Willie Walsh	□			
49) Who hosted the Late Late Show on RTE up until 1999? Pat Kenny, Ray Darcy, Darragh O`Brian, **Gay Byrne**		□		
50) Which country both hosted and won the FIFA world cup soccer finals in 1998? England, Germany, **France,** Holland		□		

	Jul93-Jun98	Jul98-Jun03	Jul03-Jun08	Jul08-Jun 09
51) Which former US President won the 2002 Nobel Peace Prize for his diplomatic work in international conflicts? **Jimmy Carter**, Ronald Reagan, George Bush, Richard Nixon		□		
52) In 1998, a bomb placed by the Real IRA exploded on a Saturday morning in which town? Newry, **Omagh**, Enniskillen, Portadown	□			
53) What was the name of the first novel written by Cecelia Ahern daughter of An Taoiseach Bertie Ahern? **PS I Love You**, The Sea, The God of Small Things, Our Fathers			□	
54) What type of structure, named after Samuel Beckett, was delivered from Holland to Dublin in May 2009? A roof, a belltower, a statue, **a bridge**				□
55) Who played the lead character in the film "Gladiator"? Brad Pitt, Denzel Washington, Harrison Ford, **Russell Crowe**		□		
56) In 2003, which country was invaded by British, American, Australian and Polish troops amid fears of it harbouring weapons of mass destruction? Afghanistan, Iran, Syria, **Iraq**			□	
57) Which soccer player left the Irish squad in the middle of the 2002 World Cup after a row with the manager in Saipan? Niall Quinn, Robbie Keane, Stephen Ireland, **Roy Keane**		□		
58) What was the name of the criminal who was extradited from the UK back to Ireland on drug trafficking charges and the suspected murder of Veronica Guerin? **John Gilligan,** Martin Cahill, Gerry Hutch, Paul Ward		□		
59) Which Irish news reporter left RTE to become a candidate for Fine Gael in the Dublin South by-election in May 2009? Brian Dobson, **George Lee,** Charlie Bird, George Hook				□
60) Name the princess who was killed in 1997 following a high speed car accident in a road tunnel in Paris? Anne, **Diana**, Margaret, Elizabeth	□			

Figure 8 Public Events Questionnaire Version 3

3.1.3.2 Content

Questions were sourced from national and international news websites. *National* events included any major news items relating to Irish politics, lifestyle, culture, weather, crime or general event excluding those to do with cultural items. *International* questions contained the same categories of news items from outside Ireland. The *Cultural* category contained both national and international events.

3.1.3.3 Updating

The questionnaire was updated every six months to adjust for long-term recruitment. This means that half of the questions in EQ1 were removed to allow for new questions from the most recent six months to be added in. As EQ1 is updated it follows that all other time periods will also update by six months.

EQ1 is made up of two six month sections, the *oldest six months* and *most recent six* months of the 12 month period. When updating, the questions in the *oldest six* months of EQ1 (7 or 8 in total) are identified and removed from EQ1. One of these questions is chosen arbitrarily to be pushed back into EQ5 in order to update EQ5. The choice of this one question depends on what category it is in and will be explained further below. When this one question is pushed back into EQ5 then one question must be pushed out of EQ5 and back into EQ10, and then out of EQ10 and into EQ15, and finally one question will be taken out of EQ 15 and left out of the new version altogether. In order to keep the balance of categories equal across each year, when the question pushed back from EQ1 to EQ5 is a *national* question it follows that all other questions being moved in this update will be *national* questions and therefore each time the questionnaire is updated it is only one category that changes in EQs 5, 10 and 15.

A pool of questions was sourced from internet news websites for each update of the questionnaire. Prospective questions were discussed at research team meetings and chosen for inclusion in the next questionnaire based on level of memorability (high) and duration of coverage of the event (brief). The research team consisted 3/4 males and 3/4 females at all times, all of whom had a minimum qualification of a third level degree, and were aged between 22 and 49. As such, it is possible that this group were not representative of the participants in the study. However as consistency with baseline was the main outcome of interest, any differences between those developing the questionnaire and those being tested on the questionnaire should not affect consistency of answering across assessment points.

3.1.3.4 Scoring and Administration

Questions were presented orally by the researcher. Participants were instructed to try recalling the answer if possible. If participants were unsuccessful at one attempt to recall the answer they were then provided with four possible answers and asked if they could recognise the correct answer from the group. If at recall stage participants recalled a wrong answer that was also one of the recognition choices, that answer was left out of the recognition choices and they were given a choice of the three remaining answers instead. This was done to avoid repetition of the incorrect answer. Participants were encouraged to guess where possible. Correctly recalled items were scored two points, recognised items one point and incorrect items scored zero points. Participants were not told whether they gave the correct answer so as to avoid a learning effect at six month follow-up.

Participants completed the assessments at baseline and at 6 month follow-up. The NART was administered at baseline only to gain a measure of current IQ. All other

assessments were administered twice, with alternate versions used for the follow-up assessment where available to minimise the occurrence of practice effects.

3.1.4 Data Analyses

Data analyses concentrated on consistency within and across each of the three versions of the Public Events Questionnaire as well as examining test-retest reliability over time. Additional secondary exploratory analyses investigate the validity of the Public Events Questionnaire.

Parallel-form reliability was examined by assessing differences between time-periods and categories across versions using one-way between groups ANOVA's. One-way repeated measures ANOVA's were used to assess internal consistency of each questionnaire by examining differences between categories and between time-periods in each version. Consistency of the proportion of items recalled and recognised across version and time-period was examined using the Chi-square test for homogeneity of variance (Shaughnessy et al., 2003). Test-retest reliability was examined using Pearson product moment correlations (r) (Pallant, 2007) and by investigating change scores between first and second assessment (Squire et al., 1989) as examined by one-way between groups ANOVA's.

Secondary exploratory analyses of construct validity of the Public Events Questionnaire examined correlations (r) between the questionnaire and age, IQ and years of education. Convergent validity was examined by correlations between measures of semantic fluency and delayed visual and verbal memory. Data were analysed using SPSS Version 16 (SPSS Inc., 2009).

3.2 Results

The data for this study were collected from 56 healthy participants, 39 of whom were female. All participants completed their first assessments between July 2008 and January 2010 and follow-up assessments between January 2009 and July 2010.

Table 3 shows means, standard deviations and range for age, NART, years of education and gender, both for the combined sample and for each version of the questionnaire.

Characteristic	n	Version 1	Version 2	Version 3	Test statistic		
					F (df)	$\chi 2$ (df)	p value
		n=25	*n=14*	*n=17*			
Age (years) mean (SD	56	34.44 (11.9)	48.75 (13.3)	39.53 (12.5)		13.06 (2)	0.001
Education (years), mean (SD)	50	16.76 (1.9)	17.5 (0.8)	17.0 (1.6)		0.953 (2)	0.621
NART, mean (SD)	56	111.36 (6.1)	111.79 (4.7)	117.41 (4.6)	6.269 (2)		0.004
Female, n (%)	56	20 (80)	13 (93)	6 (35)		14.324 (2)	0.001

Table 3: Age (years), NART, education (years) and gender of study participants

Age was not normally distributed for each version and therefore a non-parametric analysis was carried out. Age was found to be significantly different across versions. Gender ratio was also found to be significantly different across versions. No differences were found between years of education across versions (Table 3).

NART scores on Version 3 were found to be significantly higher than those on both Version 1 and Version 2, whereas Versions 1 and 2 were not significantly different (Table 3).

3.2.1 Constructing and updating the PEQ

Each version of the questionnaire consists of four time-periods: EQ1 (most recent 12 months), EQ5 (five years prior to EQ1), EQ10 (6 to 10 years prior to EQ1) and EQ15 (11 to 15 years prior to EQ1). The within version consistency across each time-period and category of the PEQ was examined, followed by across version consistency for each time-period and category. The relationship between recall and recognition scoring, by version, time-period and category was examined next. Finally the test-retest consistency of performance on the Public Events Questionnaire is examined.

3.2.1.1 Construction of the PEQ: internal consistency

Within version reliability was examined for both time-period (EQ1, EQ5, EQ10 and EQ15) and question category *(International, National* and *Cultural*). Six one-way ANOVA's were carried out comparing performance between time-periods and between categories for each version. Tukey HSD post-hoc tests and Bonferroni corrections for multiple comparisons were also conducted to show where the differences resided between each time-period and category.

With regard to differences on time-period, results for Version 1 indicate a significant difference between scores on each of the time-periods ($p<0.01$). Post hoc comparisons reveal scores on EQ10 to be significantly higher than each other time-period ($p<0.01$), while the other time-periods do not differ significantly from each other (Table 4). Scores on each time-period in Version 2 were not significantly different. No significant differences were found between scores on each time-period for Version 3.

Version	EQ1	EQ5	EQ10	EQ15	F (df)	p value
1 (n=25)	17.28 (4.95)	15.68 (3.93)	21.52 (3.66)*	17.00 (4.45)	8.754 (3)	<0.001
2 (n=14)	21.86 (2.82)	21.00 (3.78)	21.14 (3.21)	21.71 (3.47)	0.222 (3)	0.881
3 (n=17)	23.47 (2.50)	23.18 (2.53)	21.94 (3.63)	24.41 (2.94)	2.049 (3)	0.116

Table 4: Scores means (standard deviations) per time-period on each version

The amount of questions in each category were not evenly distributed for Version 1, therefore raw scores were transformed to percentage correct per category instead. Results for Version 1 showed a significant difference in performance on each category ($p<0.01$). Post hoc analyses revealed that scores for *International* questions were significantly lower than *National* questions ($p<0.01$) and *Cultural* questions ($p<0.05$). There was no difference between *National* and *Cultural* questions. Scores were highest for *National* questions, followed by *Cultural*, while lowest scores were found for *International* questions (Table 3).

A significant difference on categories was also found for Version 2 ($p<0.01$). Post hoc comparisons found that scores for *National* questions were significantly higher than both *International* questions ($p<0.05$) and *Cultural* questions ($p<0.01$). No difference was found between *International* and *Cultural* categories. No differences were found between categories for Version 3 (Table 5).

Version	National	International	Cultural	F statistic (df)	p value
1 (n=24)	66.88 (13.1)	53.17 (13.3)	64.04 (11.2)	7.922 (2)	0.001
2 (n=14)	82.71 (8.2)	68.71 (15.6)	63.36 (12.7)	8.894 (2)	0.001
3 (n=17)	81.41 (11.4)	77.94 (12.3)	74.11 (11.3)	1.660 (2)	0.201

Table 5: Scores in percentage means (standard deviations) per category on each version of the Public Events Questionnaire

3.2.1.2 Updating the PEQ: Across version reliability

Across version reliability was examined for both time-period (EQ1, EQ5, EQ10 and EQ15) and question category (*International*, *National* & *Cultural*). Consistency of performance on EQ1, EQ5, EQ10 and EQ15 across versions was examined using one-way between groups ANOVA, with Tukey HSD post-hoc analyses and Bonferroni corrections for all multiple comparisons.

Results showed a significant difference across versions for EQ1 ($p<0.01$), EQ5 ($p<0.01$) and EQ15 ($p<0.01$). No difference was found across versions for EQ10 (Table 6). Post-hoc analysis found that scores on Version 1 were significantly lower than those on Version 2 and on Version 3 for EQ1, EQ5 and EQ15; however Versions 2 and 3 are comparable on all time periods.

Time-period	Version 1	Version 2	Version3	F (df)	p value
	n=25	n=14	n=17		
EQ1	17.28 (4.95)	21.86 (2.82)	23.47 (2.50)	14.501 (2)	<0.001
EQ5	15.68 (3.93)	21.00 (3.78)	23.18 (2.53)	25.039 (2)	<0.001
EQ10	21.52 (3.66)	21.14 (3.21)	21.94 (3.63)	0.196 (2)	0.822
EQ15	17.00 (4.45)	21.71 (3.47)	24.41 (2.94)	20.167 (2)	<0.001

Table 6: Scores (means & standard deviations) per time-period on each version of the Public Events Questionnaire

Once again, scores for each category were transformed into percentages as the number of questions in each category was not evenly distributed in Version 1. Performance on *National* questions was significantly different across versions ($p<0.01$). Post hoc analyses indicated that scores on Version 1 were significantly lower than Version 2 and Version 3, however no difference was detected between *National* questions on Versions 2 and 3.

A significant difference on *International* questions was found across versions ($p<0.01$). Scores on *International* questions in Version 1 were found to be significantly lower than Version 2 and Version 3, however no difference was detected between Versions 2 and 3.

Performance on the *Cultural* category was also significantly different across versions ($p<0.05$). Post hoc analyses found a significant difference between Version 1 and Version 3 and between Version 2 and Version 3. However no difference was detected between versions 1 and 2 for the *Cultural* category (Table 7).

Version	National	International	Cultural	F (df)	p value
1 (n=24)	66.88 (13.1)	53.17 (13.3)	64.04 (11.2)	11.677 (2)	<0.001
2 (n=14)	82.71 (8.2)	68.71 (15.6)	63.36 (12.7)	17.155 (2)	<0.001
3 (n=17)	81.41 (11.4)	77.94 (12.3)	74.11 (11.3)	4.665 (2)	0.014

Table 7 Scores in percentage means (standard deviations) per category on each version of the Public Events Questionnaire

3.2.1.4 Item difficulty: recall and recognition

A chi-square test for homogeneity was used to examine whether performance on version (1/2/3) and answer type (recall/recognition/incorrect) was related. The amount (count) of answers recalled, recognised or answered incorrectly/unknown was used in this set of analyses (Table 6). Separate analyses were conducted for each time-period and for each category.

Version and score were found to be significantly related for each time-period. However the relationships between version and score were quite weak in all cases as measured with Cramer's V, a measure of association between categorical variables. Scores were re-analysed with Version 1 removed. Score type and version were still found to be significantly related for all time-periods except EQ5 (Cramer's $V=0.080$, $p>0.05$).

Similarly, version and score were found to be significantly related for each category ($p<0.01$). Again, relationships between version and answer type were weak for each category (Table 8).

Time period/ category	Recall			Recognition			Incorrect/ Unknown			p-value	Cramer's V
	V1	V2	V3	V1	V2	V3	V1	V2	V3		
EQ1	150	128	165	132	48	69	91	34	20	<0.001	0.178
EQ5	148	138	169	96	43	57	126	29	22	<0.001	0.221
EQ10	223	104	149	92	63	75	59	43	28	<0.05	0.082
EQ15	153	112	177	121	82	61	101	16	16	<0.001	0.225
National	110	206	236	69	51	80	37	23	24	<0.001	0.144
International	212	142	215	163	99	98	177	39	27	<0.001	0.203
Cultural	335	134	209	189	86	84	147	60	47	<0.01	0.012

Table 8 Counts of scores for recall, recognition and incorrect/unknown answers with Cramer's V and associated P values for chi-square for homogeneity of scoring across versions of the Public Events Questionnaire.

V1 is Version 1

V2 is Version 2

V3 is Version 3

Further analyses were undertaken to examine the relationship between versions and answer type for each time-period. Further analyses were not carried out for categories, due to the uneven amount of questions in each category in Version 1.

One-way ANOVA's (with Tukey HSD and Bonferroni corrections) indicated that there was a significant difference between the total amount of answers recalled across versions ($p<0.01$). Post hoc analyses showed that the significant differences were between Version 1 and Version 2, and also between Version 1 and Version 3 (Table 7). There was no difference in the amount of answers recalled between Versions 2 and 3.

When this was broken down by time-period significant differences were again shown for amount of answers recalled between versions for EQ1 ($p<0.01$). No differences were found between Version 2 and 3 for EQ1. In contrast, Version 1 was found to have significantly less answers recalled in EQ 1 than Version 2 or Version 3.

Significant differences in the amount of answers recalled were found for EQ5 ($p<0.01$) with Version 1found to have significantly less answers recalled than Version 2 and Version 3. No differences were found between Versions 2 and 3 for EQ5.

The amount of answers recalled was not different across versions on EQ10. For EQ15 the amount of answers recalled across versions was again significantly different ($p<0.01$). A higher amount of recall was found on EQ15 for Version 3 than either Version 1 or Version 2. In this case Versions 1 and 2 were not significantly different to each other (Table 9).

Recalled	Version 1	Version 2	Version 3	F(df)	p value
	n=25	n=14	n=17		
Total score	26.96 (8.21)	34.43 (7.49)	38.82 (6.33)	13.289 (2)	<0.001
EQ1	6.00 (3.08)	9.14 (2.45)	9.71 (1.99)	12.008 (2)	<0.001
EQ5	5.92 (2.08)	9.86 (1.56)	9.94 (1.60)	32.976 (2)	<0.001
EQ10	8.92 (2.25)	7.43 (2.37)	8.76 (2.31)	2.049 (2)	0.139
EQ15	6.12 (2.35)	8.00 (2.45)	10.41 (2.24)	17.007 (2)	<0.001

Table 9 Mean (sd) amount of answers recalled by version and time-period

There was no significant difference in the amount of answers recognised across versions when analysed by total score ($p>0.05$) (Table 10).

When this was broken down by time-period there was a significant difference in amount of answers recognised in EQ1 across versions ($p<0.05$). Version 1 had significantly more answers recognised than Version 2 on EQ1. Versions 1 and 3 and Versions 2 and 3 were comparable for EQ1.

All versions had comparable amounts of answers recognised for EQ5 and for EQ10. The amount of answers recognised in EQ15 was significantly different across versions ($p<0.05$). In Version 3 EQ15 was found to have significantly less answers recognised than Version 2, whereas Versions 1 and 2 and Versions 1 and 3 were comparable on amount of answers recognised in EQ15 (Table 10).

Recognised	Version 1	Version 2	Version 3	F(df)	p value
	n=25	n=14	n=17		
Total score	17.64 (5.4)	16.86 (5.99)	15.41 (4.43)	9.030 (2)	0.412
EQ1	5.28 (2.15)	3.42 (1.87)	4.06 (1.75)	4.442 (2)	0.016
EQ5	3.84 (1.93)	3.07 (1.59)	3.35 (1.32)	1.029 (2)	0.365
EQ10	3.68 (1.93)	4.50 (1.83)	4.41 (1.87)	1.163 (2)	0.320
EQ15	4.84 (1.67)	5.86 (2.88)	3.59 (1.97)	4.495 (2)	0.016

Table 10 Mean (sd) amount of answers recognised by version and time-period

The total scores for amount of questions answered incorrectly, or not known, were significantly different across versions ($p<0.01$). Post hoc analyses showed that the amount of incorrect/unknown answers was higher on Version 1 than Version 2, and again higher on Version 1 than Version 3. Version 2 and Version 3 were not significantly different to each other on total score for amount of answers incorrect/unknown (Table 11).

When analysed by each time-period, there was a significant difference in amount of incorrect/unknown answers in EQ1 across versions ($p<0.01$). There was a significantly higher amount of incorrect/unknown answers for Version 1 than Version 3 on EQ1. Versions 1 and 2 and Versions 2 and 3 were comparable in terms of incorrect/unknown answers on EQ1.

There was a significant difference in amount of incorrect/unknown answers in EQ5 across versions ($p<0.01$). For EQ5 Version 1 had significantly more incorrect/unknown answers than either Version 2 or Version 3. Version 2 and Version 3 did not differ significantly on amount of incorrect/unknown answers for EQ5.

Again, there were no differences across Versions for amount of incorrect/unknown answers in EQ10.

A significant difference was found across versions for amount of incorrect/unknown answers on EQ15 ($p<0.01$). Version 1 was found to have significantly more incorrect/unknown answers than either Version 2 or Version 3 on EQ15. Versions 2 and 3 did not differ in this regard (Table 11).

Incorrect/ unknown	Version 1	Version 2	Version 3	F(df)	p value
	n=25	n=14	n=17		
Total score	15.08 (6.47)	8.71 (3.58)	5.06 (3.98)	19.958 (2)	<0.001
EQ1	3.64 (2.16)	2.43 (1.69)	1.19 (0.88)	10.146 (2)	<0.001
EQ5	5.04 (2.19)	2.07 (1.07)	1.29 (1.21)	28.351 (2)	<0.001
EQ10	2.36 (1.82)	3.07 (1.69)	1.65 (1.77)	2.489 (2)	0.093
EQ15	4.04 (2.42)	1.14 (1.03)	0.94 (1.14)	18.939 (2)	<0.001

Table 11 Mean (sd) amount of answers incorrect/unknown by version and time-period

Overall, based on total score, each version was equivalent in the amount of questions recognised, while Version 1 had less answers recalled and more questions answered incorrectly/unknown than Versions 2 and 3. Versions 2 and 3 remained largely comparable when broken down by time-period, except for on EQ15, where Version 3 had more answers recalled and less answers recognised than the same time-period on Version 2.

3.2.1.6 Test-retest reliability of the PEQ

Test-retest reliability was examined in two ways: firstly by correlating scores on each version at baseline and six month follow-up; secondly by looking at change scores over time. Analyses in this section are limited to total score and time-period only.

3.2.1.6.1 Test-retest reliability

Correlations between baseline and six month follow-up scores were carried out for total score (time-periods summed) and each time-period individually. Pearson product-moment correlation coefficients (r) for each analysis are presented in Table 12. Sample sizes are given for baseline and six month follow-up respectively.

Large positive correlations were found between baseline and 6 month follow-up scores for each version and for each time-period within each version. Total score correlations at baseline and six month follow-up for all versions exceeded 0.80 which is a desirable correlation in test-retest reliability (Pallant, 2007). All other correlations were above 0.70 and significant at $p<0.01$, except for EQ1, Version 2 which was significant at $p<0.05$ ($p=0.011$). As the age of participants was significantly higher on Version 2 a partial correlation was carried out to examine if age affected this correlation. When age was controlled for the correlation between EQ1 at baseline and 6 month, on Version 2 of the questionnaire, rose to $r = 0.702$, while the significance level remained the same.

Version	Total score	EQ1	EQ5	EQ10	EQ15
1 (n=18)	0.959	0.916	0.905	0.823	0.926
2 (n=13)	0.906	0.678	0.831	0.812	0.733
3 (n=15)	0.899	0.700	0.767	0.725	0.805

Table 12 Pearson product-moment correlations between baseline and six month follow-up

3.2.1.6.3 Change over time: baseline to six month follow-up

The *amount* of change from baseline to six month follow-up within each version was examined using paired t-tests. A significant difference was found on all versions between baseline and six month follow-up performance (see Table 13). Overall, an increase of between 3.7-4.4 points above baseline performance was found at follow-up assessment. When each time-period was investigated a significant difference from baseline to follow-up was found only for EQ5 in Version 1 ($t(17) = -3.36$, $p<0.01$) and EQ5 in Version 3 ($t(15)=-3.715$, $p<0.01$), although scores in all time-periods, in each version, were higher at follow-up than baseline assessment.

Change score analyses were carried out for each time-period and compared across versions. Change scores were computed by subtracting the total score at baseline from the total score at six month follow-up. No significant differences were found between change scores on each time-period across versions (EQ1 ($F(2,43)=0.226$, $p=0.799$; EQ5 ($F(2,43)=0.053$, $p=0.948$; EQ10 ($F(2,43)=0.505$, $p=0.607$; EQ15 ($F(2,43)=0.474$, $p=0.626$), indicating change over time was comparable in each time-period across versions.

Version	Baseline	Six-month	test statistic	p value
	M (sd)	*M (sd)*	*t (df)*	
1 (n=18)	71.28 (14.7)	75.72 (17.0)	-3.721 (17)	0.002
2 (n=13)	86.53 (9.9)	90.23 (11.0)	-2.867 (12)	0.014
3 (n=15)	93.25 (9.4)	97.12 (8.7)	-4.720 (15)	<0.001

Table 13 Baseline and six-month scores on each version of the Public Events Questionnaire

3.2.3 Validity

Secondary exploratory analyses were conducted to examine the validity of the PEQ. Significance levels were set to $p<0.01$ to account for multiple testing.

3.2.3.1 Age, NART, education & gender

Correlations were carried out between performance on the combined versions of the questionnaire and age. No significant relationships were found, either for total score or for each time-period ($p<0.01$). When broken down by version, age was not correlated with Version 1 ($n=25$, $r=0.071$, $p=0.736$). A small non-significant negative correlation between age and Version 2 was found ($n=14$, $r=-0.289$, $p=0.316$). A moderate negative correlation, approaching significance, was found between age and Version 3 ($n=17$, $r=-0.483$, $p<0.05$), however this trend disappeared with the removal of one extreme outlier ($n=16$, $r=-0.398$, $p=0.196$).

Age and time-period were examined for each version and no correlations were found except for a negative correlation between age and EQ15 that approached significance on Version 3 (Table 14).

AGE*EQ		EQ1	EQ5	EQ10	EQ15
Version 1	r	0.003	0.043	0.053	0.148
	(p value)	*0.987*	*0.838*	*0.803*	*0.481*
Version 2	Pearson corr.	-0.333	-0.167	0.029	-0.416
	(p value)	*0.245*	*0.569*	*0.922*	*0.139*
Version 3	Pearson corr.	-0.046	-0.296	-0.133	-0.598
	(p value)	*0.867*	*0.265*	*0.624*	*0.014*

Table 14 Age and time-period Pearson product-moment correlations (r)

NART scores were correlated with total score and each time-period for the three versions of the questionnaire combined. Significant positive correlations were found for total score and EQ1 ($r=0.557$, $p<0.01$), EQ5 ($r=0.554$, $p<0.01$) and EQ15 ($r=0.499$, $p<0.01$). The correlation between combined performance on EQ10 and NART approached significance ($r=0.301$, $p=0.024$). When examined by version, scores on Version 1 were significantly positively correlated with scores on the NART ($n=25$, $r=0.670$, $p<0.01$). Scores on Version 2 ($n=14$, $r=0.335$, $p=0.242$) and version 3 ($n=17$, $r=0.312$, $p=0.223$) showed smaller, non-significant correlations with scores on the NART.

Education, measured in years, was not significantly correlated with any time-period or total score when the three versions were combined ($p<0.01$). When examined by version, education was found to be weakly but non-significantly correlated with scores on Version 1 ($n=25$, $r=0.223$, $p=0.284$) and Version 3 ($n=17$, $r=0.221$, $p=0.394$). Data on years of education was only available for 8 participants on Version 2, where a moderate, but again not significant, correlation was found ($n=8$, $r=0.314$, $p=0.449$).

Independent t-tests were used to examine differences in performance owing to gender. The significance level was again set to $p<0.01$ to correct for multiple testing. When performance of males and females from the three versions were combined no significant differences were found between genders on EQ1, EQ5 or EQ10, although all three approached significance ($p<0.05$). A significant difference was found for EQ15 and for total score ($p<0.01$), when versions were combined. In all cases males scored higher than females (Table 15). Data for Version 2 was removed as there was only one male participant in this group, and results were re-analysed. Gender differences were subsequently found to be significant on EQ1, EQ5, EQ15 and total score ($p<0.01$), again with males performing better than females. When versions were analysed

separately (for Version 1 and 3 only) no significant differences were found between performances of males and females on any time-period versions, although EQ15 on Version 1 approached significance ($p<0.05$-Table 15).

	Gender (n)	EQ1	EQ5	EQ10	EQ15	EQ Total
Combined (1, 2, 3)	**M (17)**	22.29	21.41	22.94	23.35	89.71
		(3.65)	*(4.42)*	*(3.07)*	*(3.18)*	*(11.60)*
	F (38)	19.43	18.36	20.95	19.15	77.85
		(4.90)	*(4.76)*	*(3.53)*	*(5.10)*	*(14.95)*
p value		**0.036**	**0.028**	**0.049**	**0.003**	**0.005**
Combined (1 & 3)	**M (16)**	22.31	21.38	23.00	23.50	89.88
		(3.77)	*(4.56)*	*(3.16)*	*(3.22)*	*(11.96)*
	F (26)	18.23	17.08	20.88	17.84	74.00
		(5.28)	*(4.68)*	*(3.69)*	*(5.28)*	*(15.53)*
p value		**0.006**	**0.006**	**0.065**	**<0.001**	**0.001**
Version 1	**M (5)**	18.60	17.00	22.80	20.80	78.20
		(3.20)	*(4.63)*	*(2.77)*	*(2.39)*	*(7.63)*
	F (20)	16.95	15.35	21.20	16.05	69.50
		(5.31)	*(3.80)*	*(3.85)*	*(4.37)*	*(14.50)*
p value		**0.516**	**0.413**	**0.394**	**0.030**	**0.212**
Version 3	**M (11)**	24.00	23.36	23.09	24.73	95.18
		(2.68)	*(2.94)*	*(3.44)*	*(2.83)*	*(9.60)*
	F (6)	22.50	22.83	19.83	23.83	89.00
		(1.97)	*(1.72)*	*(3.19)*	*(3.31)*	*(7.46)*
p value		**0.250**	**0.693**	**0.076**	**0.566**	**0.193**

Table 15 Means (standard deviations) of males and females performance on time periods of the Public Events Questionnaire

When versions were combined to assess categories, males were found to perform significantly better than females on *International* questions ($p<0.01$), while performance on *Cultural* questions approached significance ($p<0.05$) with males again scoring higher than females. No differences were found for *National* questions. With Version 2 removed the significant difference for males and females persisted for *International* questions and the difference for *Cultural* questions became significant ($p<0.01$). When broken down by version, there were no significant differences in any category between males and females for Version 1 or 3, however *International* questions in Version 3 approached significance ($p>0.05$) (Table 16).

	Gender	National	International	Cultural
Combined	M (17)	78.06	75.53	72.65
(1, 2, 3)		*13.56*	*14.66*	*11.12*
	F (38)	74.21	59.97	64.45
		13.67	*16.29*	*12.19*
p value		**0.338**	**0.001**	**0.022**
Combined	M (16)	77.63	75.06	74.06
(1 & 2)		*13.89*	*15.01*	*9.77*
	F (25)	69.88	56.00	64.48
		13.95	*15.42*	*12.25*
p value		**0.090**	**<0.001**	**0.012**
Version 1	M (5)	70.20	58.60	70.80
		12.03	*7.83*	*8.23*
	F (19)	66.00	51.74	62.26
		13.59	*14.26*	*11.36*
p value		**0.537**	**0.317**	**0.132**
Version 3	M (11)	81.00	82.54	75.54
		13.83	*10.78*	*10.41*
	F (6)	82.17	69.5	71.50
		5.49	*11.04*	*13.37*
p value		**0.809**	**0.032**	**0.498**

Table 16 Means (sd) of males and females performance on categories of the Public Events Questionnaire

3.2.3.3 Semantic fluency and delayed recall

In line with its purported function to measure semantic memory we looked at correlation of the Public Events Questionnaire with category fluency. Weak and non-significant correlations were found between semantic fluency and Version 1 (n=25, r=0.250, p=0.228) and Version 2 (n=8, r=0.253, p=0.546) while no correlation was found between semantic fluency and Version 3 (n=17, r=0.083, p=0.753).

As a measure of long-term memory we looked at correlations between the Public Events Questionnaire and delayed verbal and visual memory, as measured by the Buschke Free and Cued Selective Reminding Test (FCSR) delayed recall task and the Rey-Osterreith Complex Figure (ROCF) delayed recall components respectively. Version 3 was not examined here as only two participants completed the Buschke FCSR and ROCF in that group. No correlations were found between Version 1 and delayed verbal recall (n=25, r=0.118, p=0.574). Moderate, but non-significant, correlations were found between Version 2 and delayed verbal recall (n=8, r=0.560, p=0.149). A further analyses was carried out to examine the relationship between free recall on the Public Events Questionnaire (a score of "2") and free delayed recall on the Buschke FCSR. No significant correlations were found.

No correlation was found between delayed visual recall and Version 1 (n=25, r=0.012, p=0.953) or delayed visual recall and Version 2 (n=8, r=0.485, p=0.223).

3.3 Discussion

In this chapter the performance of participants from a normal population on a Public Events Questionnaire was examined. The aim was to develop a generalisible method of constructing and updating a Public Events Questionnaire that can be tailored for use with specific populations. Reliability both within and across versions was examined, as was item difficulty and test-retest performance over a six month time-period. Secondary exploratory analyses were carried out to examine validity of the Public Events Questionnaire.

Main findings from the analyses conducted indicated that Versions 2 and 3 of the Public Events Questionnaire are reliable across and within versions for all time-periods and are comparable on levels of recall and recognition. Findings relating to performance on categories were mixed across and within versions. Change over time was not significantly different across each version of the Public Events Questionnaire. The limited validity analyses suggested that the Public Events Questionnaire may be affected by age and IQ (NART), however these were not conclusive. These findings will now be discussed in more detail.

3.3.1 Construction and updating of the Public events Questionnaire

As mentioned in the methods section the format of construction of the Public Events Questionnaire was changed between Version 1 and 2. The main change involved ensuring each time-period contained an equal amount of questions from each category, which were spread equally across each year. This change was applied in order to equally assess performance in each category, and to permit ease of updating for subsequent versions. This approach allowed me to examine reliability of the Public

Events Questionnaire when constructed and updated in a standardised manner (i.e. Versions 2 and 3), compared to a less strictly compiled questionnaire. The resulting differences in consistency between Version 1 and Versions 2 and 3, and the comparability of Versions 2 and 3, reflect this change and support the construction and updating of Public Events Questionnaire's following the standardised method described. This was especially successful for comparability on time-periods, where Versions 2 and 3 were found to be comparable within each version. Three of the four time-periods within Version 1 were also comparable to each other; however, performance on one time-period, EQ10, was significantly better than the other three.

The within version reliability indicates that the questionnaires are reliably constructed, and therefore we can expect participants to show the same level of performance on different sections of each questionnaire. This would be important for investigating memories from specific time-periods. Versions 2 and 3 were also found to be comparable across each version. In Version 1, EQ10 was comparable to Versions 2 and 3, however performance on all other time-periods on Version 1 was significantly worse than the other versions. This, along with the finding that three out of four time-periods within Version 1 produced significantly lower scores than EQ10 suggests that questions on Version 1, in particular for sections EQ1, EQ5 and EQ15, were more difficult than updated versions. However, demographic differences in groups may have contributed to this finding. Scores on the NART for participants who completed Version 1 were lower than those of participants on Versions 2 and 3, though only significantly different to Version 3. Age was also lower for Version 1, compared to Versions 2 and 3. Gender was also unevenly distributed across groups and results indicated that males performed better than females in general. However as there was a higher percentage of

males on Version 1 than Version 2 gender does not explain the poorer performance on Version 1.

With regard to categories the picture was less clear-cut both across and within versions. Significant differences between categories were detected within Version 1 and within Version 2, but not within Version 3. Within Version 1 *International* questions scored significantly lower than each other category, whereas within Version 2 *National* questions scored significantly higher than other categories. Overall, *National* questions scored highest across all three versions. In versions 2 and 3 *International* questions scored second highest with *Cultural* questions scoring lowest. For Version 1 *Cultural* questions scored second highest while *International* questions scored lowest.

Across versions, performance on *National* and *International* categories was significantly lower for Version 1, than either Versions 2 or 3, which were comparable. Performance on the *Cultural* category was significantly higher for Version 3 than either Version 1 or 2, while versions 1 and 2 were not significantly different.

3.3.2 Item difficulty

A further indication that Version 1 might simply have been more difficult than the other versions was found when looking at differences in amounts of questions recalled, recognised or incorrect/unknown in each version. A significant, but weak, relationship was demonstrated between proportions of answers correctly recalled or recognised and version of the Public Events Questionnaire completed. Version 1 was found to have lower levels of recall than either Version 2 or 3, which did not differ on recall levels. Version 1 also showed significantly more "incorrect/unknown" answering than both other versions, whereas Versions 2 and 3 were comparable. This finding again suggests that questions on Version 1 were more difficult than those on Versions 2 and 3. The

finding that proportions of answers recalled, recognised or answered incorrectly depended on version, and the persistence of this effect for 3 out of 4 time-periods when Version 1 was removed, was somewhat surprising given the degree of consistency between Versions 2 and 3. However, for each time-period the level of dependence on version was found to be weak. As no other studies have reported findings for different versions of a public events questionnaire, further study will be necessary to investigate what factors contribute to the relationship between version and performance.

Item difficulty in each version was also assessed for categories, and again it was found that answer type (recall/recognition/incorrect) for each category was significantly related to each version of the questionnaire. This is not surprising given the variability of performance on each category within each questionnaire, as discussed previously.

3.3.3 Test-retest reliability

Despite the inconsistencies found for Version 1, analyses of test-retest reliability demonstrated highly consistent performance from baseline to follow-up assessment for all three versions of the Public Events Questionnaire, where strong, significant, correlations between baseline and six month follow-up scores were demonstrated. Only one time-period (EQ1, Version 2) showed a weak correlation (i.e. $r < 0.7$), however when age was controlled for (owing to its being significantly higher on Version 2 than Versions 1 or 3), this improved to $r > 0.7$. Correlations between total scores on each version were above 0.80, thus supporting the use of this questionnaire for repeated testing (Pallant, 2007).

The change in performance from initial assessment to follow-up assessment was significant for each version of the questionnaire; however, change scores from baseline to follow-up did not differ across versions. This practice effect may be a result of the

cued recognition component of the test, whereby cueing the correct answer makes that answer more available for recall at further testing sessions. Nonetheless, these findings are particularly important when the aim of the assessment is to determine how memory has changed from one time-point to another. Although there has not been much previous research on this point, our findings are in line with those from two earlier studies that found strong correlations for test-retest reliability and little change in performance over time in public events memory (Bizzozero et al., 2004, Squire, 1975) and indicate that this Public Events Questionnaire is a reliable method of assessing consistency of public events memory over time.

3.3.4 Validity of the Public Events Questionnaire

Limited validity analyses were performed to assess whether performance on a Public Events Questionnaire was linked to demographic characteristics such as age, sex, IQ or education as these have been associated with Public Events Questionnaires previously (Bizzozero et al., 2004, Howes and Katz, 1988, Squire, 1975). Relationships with measures of semantic and long-term memory were also investigated.

When results were pooled for all versions, age was not significantly correlated with performance. A trend towards poorer performance with increasing age was found for Versions 2 and 3 of the questionnaire, with moderate correlations found between the most remote time-period (EQ15) and age for Versions 2 and 3. Although these correlations were not significant, this finding is in line with previous studies (Warrington and Sanders, 1971). Moderate negative correlations between age and performance on more recent time-periods (EQ1, Version 2 and EQ5, Version 3) were also uncovered, although these were not significant. However, the finding of poorer

performance of older participants on recent events is again in line with some previous studies (Howes and Katz, 1988, Squire and Slater, 1975).

The combined scores from each version were found to be significantly correlated with NART scores, for total score and each time-period separately. When broken down by version, a significant and large positive correlation was found between the NART and Version 1 of the Public Events Questionnaire. Versions 2 and 3 showed moderate but non-significant correlations with the NART. These findings suggest that IQ may be a factor in Public Events Questionnaire performance, with higher IQ suggesting better performance. This finding may also explain some of the lower scoring on Version 1 of the questionnaire, as NART scores were lowest in this group. However, this must be viewed with caution due to the non-significance of findings for Versions 2 and 3. Nonetheless, this is in line with previous research that has found intelligence to be linked to public events memory (Howes and Katz, 1988, Meeter et al., 2010).

The relationship between Public Events Questionnaire scores and years of education was also investigated. Scores from the three versions combined were not related to education. When examined by version, weak to moderate non-significant correlations were found between years of education for Versions 1 and 3, while a moderate, non-significant, relationship was found for Version 2. The stronger relationship found on Version 2 may be due to the fact that this group was highly educated, with the minimum years of education being very high (≥17 years), and the small sample size (n=8) used in this particular analysis.

With regard to gender differences, males were generally found to perform better than females, on all time-periods and on *International* and *Cultural* categories. This is in line with previous studies which have found males are better at recalled news items than females (Botwinick and Storandt, 1980, O'Connor et al., 2000, Meeter et al., 2010).

When Version 1 and 3 were combined, with Version 2 omitted, these differences became greater still. However when individual versions were examined these differences largely disappeared, except for Version 1, EQ15 and Version 3 *International* questions which approached significance. This would suggest that gender differences were not found within versions, but across versions, indicating that question difficulty, rather than gender per se, affected performance.

Secondly, correlations between the Public Events Questionnaire and measures of delayed memory were examined to investigate the validity of the Public Events Questionnaire as a measure of long-term memory function. It should be noted that delayed memory tests were anterograde in nature, as opposed to retrospective as per the Public Events Questionnaire. Nonetheless, the anterograde items were included as a measure of items in long-term memory. In this set of analyses Version 3 could not be examined due to low numbers of participants completing the Buschke FCSR test and ROCF in this group. This was due to the assessment battery being shortened at this point in the study to ensure a high uptake of the repeat assessment, thus prioritising reliability over validity analyses. No correlations were found between either verbal or visual delayed recall and Public Events Questionnaire scores on Version 1. Moderate to strong correlations were found for both verbal and visual delayed memory and scores on Version 2 of the Public Events Questionnaire. The difference between findings for Version 1 and Version 2 may be related to the different construction of each questionnaire and therefore conclusions cannot be drawn here regarding the use of the Public Events Questionnaire as a measure of long-term memory, although further study with versions constructed as per Version 2 may provide support for this. The finding that free delayed recall on the Buschke FCSR and amount of questions recalled was not correlated indicates that free recall on the Public Events Questionnaire is not the same

as delayed free recall of recently learned information. This is not entirely surprising as the Buschke FCSR is an anterograde memory test of verbal material which, although linked with particular categories to enhance recall, most likely has fewer contexts than a public event, and therefore differs in its composition. Previous studies have shown participants do better at recalling schematic or conceptually based information that is integrated into a framework with other information, than recall of discrete facts (O'Connor et al., 2000, Conway et al., 1992, Semb and Ellis, 1994).

Finally, correlations between the Public Events Questionnaire and a measure of semantic fluency were examined, in line with episodic/semantic conceptual divisions in the literature. Here evidence of only a weak non-significant relationship was found between semantic fluency and scores on the Public Events Questionnaire.

Overall, the limited validity analyses conducted here would suggest that when public events questionnaires are constructed and updated in a standardised manner they may be useful for examining long-term memory in general. In addition, in line with previous findings gender and NART scores may be related to performance on these tests.

3.3.5 Limitations, strengths and future directions

As a method of test construction this study has limitations. One limitation is the small sample sizes assessed on each version of the Public Events Questionnaire and differences between age, gender and NART scores on each version. This was due to the fact that the controls used in the current reliability and validity analyses were also being recruited for the overall assessment in the Mem-Dep study, which assessed a range of cognitive functions over six and twelve months follow-up. Due to the required commitment of three testing occasions over twelve months, recruitment was slower than

anticipated, and this coupled with the fact that the questionnaire had to change every six months, meant numbers on each version were limited. A second limiting factor was the change in format between Version 1 and subsequent versions of the Public Events Questionnaire. However, as shown, the standardised development of Versions 2 and 3 resulted in good reliability, both within and across versions, and test-retest reliability was good across all three versions. A third limitation relates to practice effects when the same version of the questionnaire is used with the same participants at follow-up assessments. The nature of the question of interest in this study (i.e. does the participant still remember what they remembered at initial testing?) makes it impossible to use an alternate version of the questionnaire in this instance, however this could be addressed when using the questionnaire with a clinical population by using a control group at each testing point.

However, as stated earlier, this questionnaire was not designed to test the theory of public events memory in depth, but instead to provide a measure of the consistency of public events memory, and retrospective memory in general, over a period of time. The analyses relating to internal consistency, parallel version reliability and item difficulty suggest that this questionnaire is reliable when constructed in a standardised manner. In addition, the test-retest reliability of the questionnaire is good across all versions of the questionnaire.

Future studies that aim to assess verifiable long-term memory with a public events questionnaire would be encouraged to develop such questionnaires in a similar manner to the method outlined here. With regards to validity, it is also recommended to administer a short questionnaire regarding level of interest in the media to participants along with the Public Events Questionnaire, as this has been shown to be highly correlated with public events memory (Howes and Katz, 1988, Meeter et al., 2010).

This research was conducted as part of a larger study where the main purpose of the Public Events Questionnaire was to gain a measure of the consistency of public events memory over time, and throughout depressive illness and treatment. This test, therefore, is suitable for assessment of memory change over time, in both healthy and clinical populations, where memory may be affected over the course and treatment of an illness. The following chapters will describe the use of the Public Events Questionnaire as part of a neurocognitive battery of tests used to assess cognitive functioning during treatment for a major depressive episode, treated either with pharmacotherapy or electroconvulsive therapy, and over long-term follow-up of six to twelve months.

CHAPTER 4: RETROSPECTIVE MEMORY AND GENERAL COGNITION IN DEPRESSION: ACUTE PHASE AND 2 MONTH FOLLOW-UP

4.1 Introduction

Impairments of cognitive function have been consistently reported as symptoms of depression. Indeed, symptoms such as difficulties concentrating and complaints of poor memory are common in Major Depressive Disorder (MDD) and are listed as one of the criteria that may be met in diagnosing the disorder (American Psychiatric Association, 2000). As previously described above (section 1.2) studies have found that patients can exhibit a range of cognitive impairments, including disruptions to attention, psychomotor activity, executive function and various memory processes during a depressive episode (Austin et al., 2001). However, it is not clear whether the impairments are due to the depressed state, in which mood affects cognition, or to some endogenous trait in individuals who suffer from depressive disorder.

Previous studies that looked at the effects of depression on cognition during an episode of depression have found that attentional deficits are apparent in effortful tasks of attention (Farrin et al., 2003, Gualtieri et al., 2006, Zakzanis et al., 1998) as well as in tasks involving executive function (Austin et al., 2001, Douglas et al., 2011, McDermott and Ebmeier, 2009, Stordal et al., 2004). For psychomotor functions, studies have found depressed patients to be impaired relative to controls on measures of reaction time (Kertzmana et al., 2010, Pier et al., 2004). Anterograde memory, both verbal and visual, is also commonly found to be impaired during a depressive episode (Austin et al., 2001, Bearden et al., 2005, Douglas et al., 2011, Gallassi et al., 2006, Veiel, 1997, Zakzanis et al., 1998).

Studies have also examined whether cognition improves or remains impaired when patients are treated for depression. Although attention has been found to improve with improvement in mood, in euthymic patients and patients followed up less than six month after initial assessment deficits may remain relative to controls (Douglas et al., 2011, Paelecke-Habermann et al., 2005, Weiland-Fiedler et al., 2004). In contrast, psychomotor function has been shown to return to the level of controls at follow-up of up to six months (Douglas et al., 2011, Gallagher et al., 2007). With regard to executive functions, some studies have shown a significant increase in performance upon remission of depressed mood (Beblo et al., 1999, Jaeger et al., 2006), however deficits have been shown to persist in euthymic patients compared to controls (Paelecke-Habermann et al., 2005, Paradiso et al., 1997). Follow-up assessments have shown mixed results with regard to anterograde memory, both verbal and visual, when the depression is remitted, with some studies showing no improvement at six month follow-up (Gallassi et al., 2006), while others found remitted patients improved relative to non-remitted patients (Gallagher et al., 2007). Public events memory has not been found to be impaired at follow-up compared to baseline and to controls (Calev et al., 1989, Gallassi et al., 2006). In contrast to this performance on autobiographical memory has been shown to be significantly impaired in remitted depressed patients compared to controls at follow-up (Gallassi et al., 2006).

While interest in the area of cognitive functioning in depression has increased in recent years there are still limitations in studies carried out to date. Many studies do not assess retrospective memory function alongside other general cognitive functions such as anterograde memory, attention, psychomotor processing and executive functioning (Austin et al., 2001, Beblo et al., 1999, Biringer et al., 2007, Douglas and Porter, 2009, Gualtieri et al., 2006, Porter et al., 2003). Those that do examine retrospective memory

tend to focus specifically on overgeneral autobiographical memory in the absence of any other cognitive function. The current study aims to add to the current literature and moreover to provide information about the functioning of retrospective memory, for both autobiographical and public events information, in major depressive disorder (MDD). For this reason, the memory functions are discussed separately to the rest of the cognitive functions in the following chapters. However it should be understood that this is in order to examine memory functions in more depth and they are still understood to be a cognitive function themselves. Also notable is that previous research has often reported data from samples with mixed depressive diagnosis (unipolar or bipolar depression) or has not specified the exact depressive diagnoses of participants (Abas et al., 1990, Beblo et al., 1999, Jaeger et al., 2006, Trichard et al., 1995). In order to control for any confounding effects of different depressive diagnoses all participants included in this study had a diagnosis or unipolar depression, with no co-morbid diagnoses. In addition to this, many studies include participants who have received previous electroconvulsive therapy (ECT), providing that the ECT has not been received in the last six months. Due to the on-going debate regarding the effects of ECT on memory function and some evidence of persisting deficits in retrospective memory function (Lisanby et al., 2000, Sackeim et al., 1993, Sackeim et al., 2000, Sackeim et al., 2007, Squire and Slater, 1983, Squire et al., 1981) it was deemed important to exclude any participants with previous ECT in the current study, thus further limiting the effects of any confounding variables and adding to the integrity of the sample.

In this section of the study the following hypotheses were examined:

1. At baseline, autobiographical memory function will be worse in depressed participants than healthy controls, whereas public events memory function will be equivalent for both groups.

2. At baseline depressed participants will perform worse than controls on measures of attention, executive function and psychomotor speed and processing.
3. Performance on measures of retrospective memory and general cognitive function will improve over time as depression severity decreases.

4.2 Methods

4.2.1 Design

The Mem-Dep study was designed to investigate the effect of depression, both during an acute episode and after treatment for up to one year, on retrospective memory function and general cognitive function such as verbal and visual learning and memory, attention, psychomotor processing and executive function. It is a between group case-control study with a repeated measures design. This section of the Mem-Dep study focused on performance of participants in the depressed group compared to that of healthy controls at baseline. This was followed by a comparison of baseline and two month follow-up cognitive functioning in the depressed group. This study took place under real-world conditions and all depressed participants remained on medication as prescribed by their treating consultant.

4.2.2 Ethics and consent

Full ethical approval was granted for this study by the St. Patrick's University Hospital Research Ethics Committee (Protocol number 01/08-Appendix 19) and the Trinity College Dublin, School of Medicine, Faculty of Health Sciences Research Ethics Committee (Appendix 20).

4.2.3 Participants

Participants in the depressed group were patients ≥18 years admitted to St. Patrick's University Hospital or St. Edmundsbury Hospital with unipolar major depressive disorder (diagnosis confirmed using Structured Clinical Interview for Diagnostic and Statistical Manual, fourth edition (DSM IV (American Psychiatric Association, 2000)), Axis 1 (SCID-1 (First et al., 1995)) and a Hamilton Depression Rating Scale 24-item (HDRS-24) (Hamilton, 1960, Kovacs et al., 1981) score of ≥ 21. Participants could not have a co-morbid psychiatric diagnosis, except where anxiety was diagnosed secondary to major depressive disorder. All participants required English as their first language. Exclusion criteria comprised diagnosis of dementia or other comorbid disorder as assessed by the Diagnostic and Statistical Manual Axis 1 diagnosis; alcohol/other substance abuse in previous six months; past history of treatment with ECT; major sensory deficit; inability/refusal to consent.

Participants in the control group were aged ≥ 18; had English as first language; had a HDRS-24 score of ≤8 and Mini Mental State Examination (MMSE) ≥26 (Folstein et al., 1975). Controls were excluded from participation if they had any past psychiatric history; previous ECT; current major medical illness/major sensory deficit; alcohol/other substance abuse in previous six months; or inability/refusal to consent.

4.2.4 Procedure

Once consenting participants met relevant inclusion and exclusion criteria the neuropsychological testing was carried out. Standardised neuropsychological and

clinical assessments were used where possible and participants were encouraged to complete all assessments, unless unable to do so. The test battery included clinical assessments of depression severity (HDRS-24, Beck Depression Inventory, Version 2 (BDI-II (Beck et al., 1996)) and general psychopathology (Brief Psychiatric Rating Scale (BPRS (Overall and Gorham, 1962)). In addition, cognitive assessments covered global cognitive function (Addenbrooke's Cognitive Examination, revised (ACE-R (Mioshi et al., 2006) and MMSE), retrospective memory (Columbia Autobiographical Memory Interview, short-form (AMI-SF (McElhiney et al., 1997, McElhiney et al., 1995)) and the Public Events Questionnaire), verbal learning and memory (Buschke Free and Cued Selective Recall (FCSR Buschke and Fuld, 1974)), visual learning and memory (Rey-Osterrieth Complex Figure (ROCF (Loring and Meador, 2003, Osterrieth, 1944, Rey, 1941, Taylor, 1979), attention and working memory (Digit Span Forwards and Backwards (Wechsler, 1981), psychomotor speed and processing (Grooved Pegboard Test (Klove, 1963) and Trail Making Test Part A (TMT-A (Army Individual Test Battery, 1944)) and executive function (Trail Making Test Part B (TMT-B (Army Individual Test Battery, 1944) and fluencies from the ACE-R). Tests took approximately two hours to complete. The researcher was present at all times and guided participants through all assessments. All participants completed the assessment battery at baseline, and those in the depressed group repeated the assessment two months after baseline.

4.2.5 Data analyses

Data were assessed for normality, with non-parametric alternatives used for each test if data were not normally distributed. Independent t-tests were used to assess

differences between groups at baseline. Paired t-tests were used to assess differences in the depressed group between baseline and two month follow-up assessment. Correlation analyses (Pearson's product moment (r) or Spearman's rho as appropriate) were carried out to investigate relationships between depression severity and cognitive function at two month follow-up.

4.3 Results

4.3.1 Acute effects of depression: baseline comparisons of depressed and healthy control participants

Participant recruitment took place between July 2008 and February 2010. A total of 29 depressed participants and 37 control participants were recruited and completed baseline assessments (Figures 9 and 10).

Depressed participants remained on all prescribed medications throughout the study. Psychotropic medications at baseline are presented in Table 17.

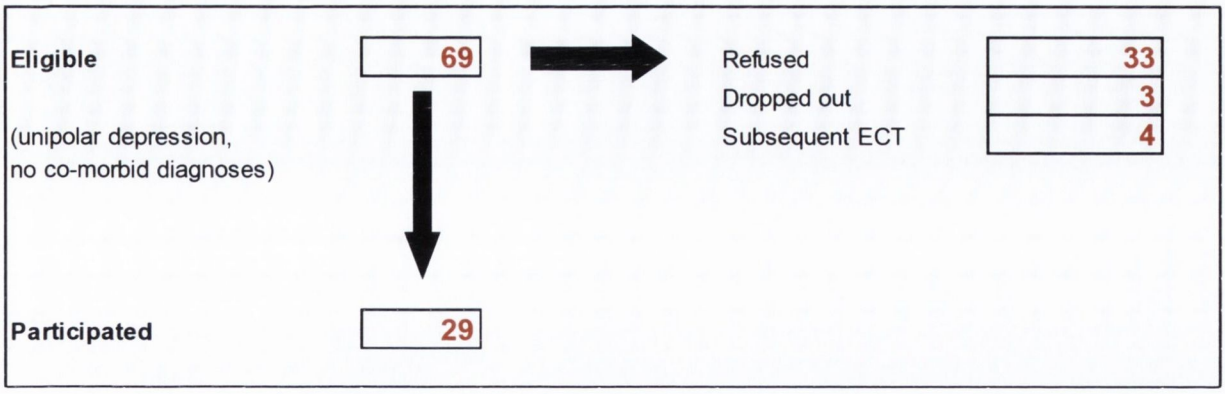


Figure 9 Depressed participant recruitment

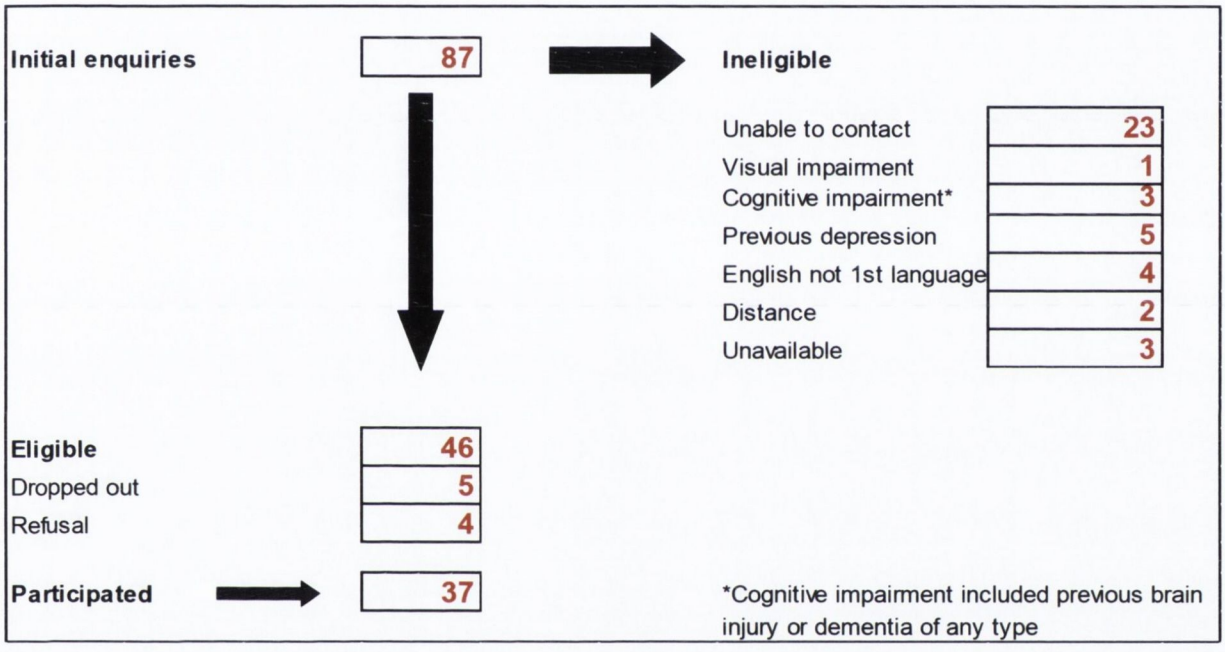


Figure 10 Control participant recruitment

Medications- depressed participants

Psychotropic medications:	*N*	*%*
Selective Serotonin Re-uptake Inhibitors	12	41
Serotonin Noradrenaline Re-uptake Inhibitors	11	38
Monoamine Oxidase Inhibitors	0	0
Tricyclic Antidepressants	5	17
Noradrenaline and Specific Serotonin antidepressants	4	14
Benzodiazepines	7	24
Lithium	3	10
Anti-convulsants	2	7
Anti-psychotics	6	21
Non-benzodiazepine hypnotics	13	45
Other	4	14

Table 17 Depressed group psychotropic medications at baseline

4.3.1.2 Demographic differences at baseline

Demographic differences between groups were assessed using independent t-tests and chi-square analyses. Values are presented in Table 18. From the depressed group four participants did not complete the NART due to a diagnosis of dyslexia. No difference was found between depressed and control groups for scores on the NART. The groups were significantly different at baseline on age in years, level of education and gender.

Characteristic		Depressed Group	Control Group	Test statistic t (df)	Test statistic $\chi 2$ (df)	p value
		n=29	*n=37*			
Age (years)- mean (SD)		46.7 (12.2)	39.4 (13.7)	2.282 (64)		0.026
NART- mean (SD)		112.9 (7.0)	112.5 (5.8)	0.207 (64)		0.836
Education (level)	1	0 (0)	1 (2.7)		10.205 (3)	0.017
	2	11 (37.9)	3 (8.1)			
	3	15 (51.7)	23 (62.2)			
	4	3 (10.3)	10 (27)			
Female- n (%)		15 (51.7)	29 (78.4)		4.067 (1)	0.044
HDRS-24- mean (SD)		29.6 (5.9)	3.4 (2.3)	24.537 (64)		<0.001
Previous ECT		None	/			
Treatment resistant n (%)		1 (3.4)	/			

Table 18 Baseline characteristics of the depressed and control Mem-Dep participants

4.3.1.3 Clinical and cognitive performance at baseline

Differences in mood and cognition between the depressed and control groups were assessed using independent t-tests (t), or Mann-Whitney U tests (z) as a non-parametric alternative where data were not normally distributed. Relationships between clinical and cognitive tests with each group were also investigated using Pearson's product moment correlation (r) or Spearman's rho where appropriate. Partial correlations, which control for the effects of one variable while looking at the relationship between another two variables, were carried out to assess the impact of age, gender and education on performance across groups because of the baseline differences between groups on the variables. A more stringent significant value of $p<0.01$ was adopted for all analyses to control for effects of multiple testing. In some cases participants were not able to complete all assessments due to fatigue or time constraint, resulting in a lower number of assessments available for analysis for some clinical and cognitive measures.

4.3.1.3.1 Clinical differences at baseline

Depressed patients scored significantly higher (i.e. more depressed) than control participants on all measures of depression severity, including the HDRS-24, BDI-II and BPRS (Table 19, Figures 11, 12, 13). Correlations carried out to assess the relationship between group and performance on each clinical measure were also significant ($p<0.001$), and remained significant when age, sex and education were controlled for ($p<0.001$).

Measure	Depressed group	Control group	t (df)	z	p value
	n=29	n=37			
HDRS-24	29.59 (5.9)	3.35 (2.3)	24.357 (64)		<0.001
BDI-II	32.28 (13.2)	2.30 (2.95)		-6.893	<0.001
BPRS	29.76 (4.4)	19.14 (1.1)		-6.614	<0.001

Table 19 Mean scores (SD) on the Hamilton Depression Rating Scale, 24 item, the Beck-Depression Inventory-II and the Brief Psychotic Rating Scale for depressed and control participants at baseline

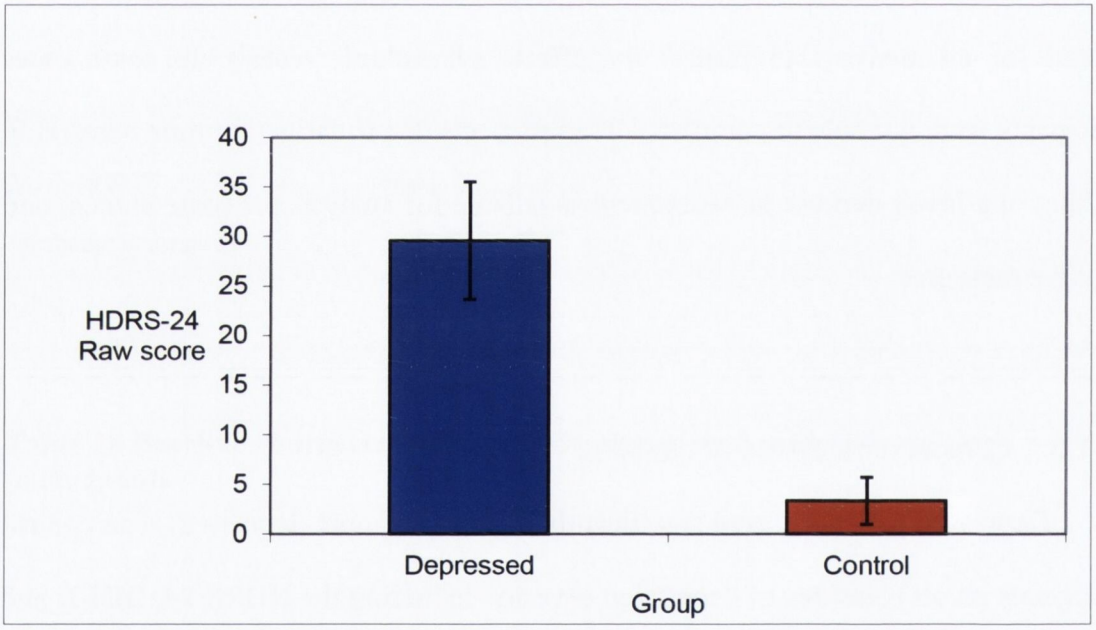


Figure 11 Scores on the Hamilton Depression Rating Scale, 24 item for depressed and control participants at baseline

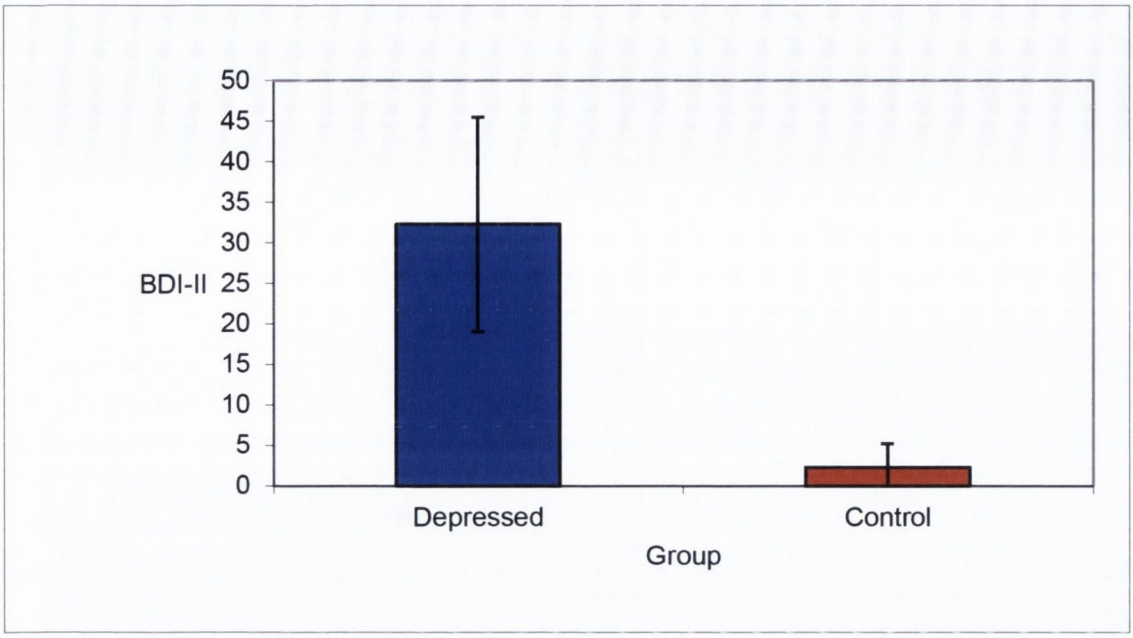


Figure 12 Scores on the Beck Depression Inventory-II for depressed and control participants at baseline

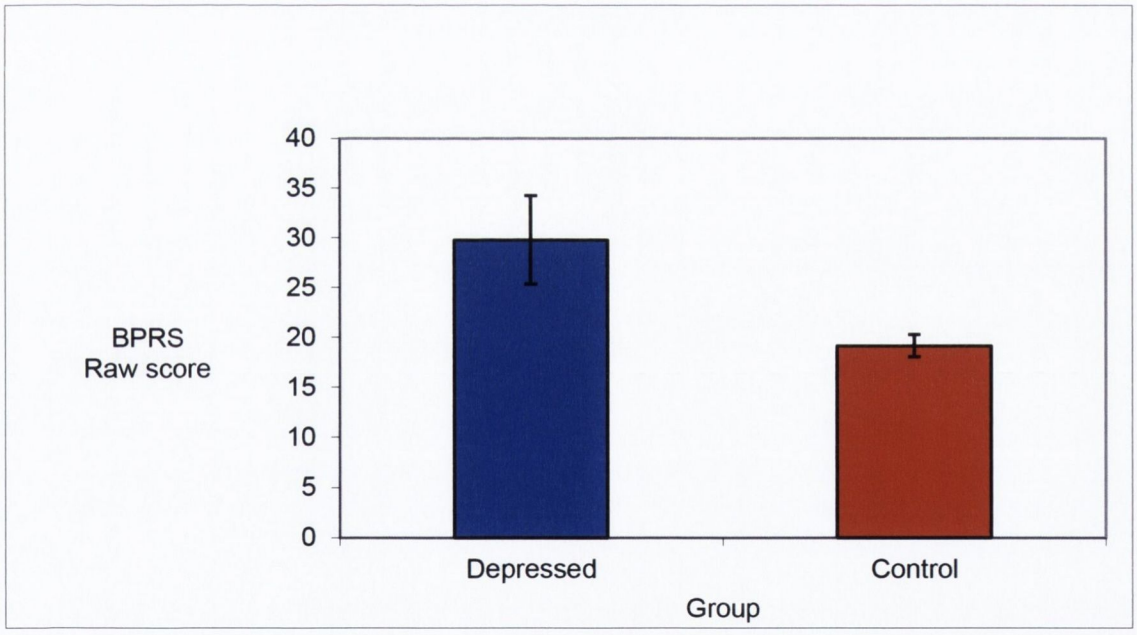


Figure 13 Scores on the Brief Psychiatric Rating Scale for depressed and control participants at baseline

4.3.1.3.2 Differences in retrospective memory and cognitive function at baseline

Results are grouped by type of cognitive function investigated beginning with global cognitive function, followed by retrospective memory function, anterograde memory function, attention, psychomotor speed and processing and executive function.

4.3.1.3.2.1 Global Cognitive function

The difference between depressed and control participants approached significance for the ACE-R with control participants scoring higher than depressed patients (Table 20, Figure 14). However, correlation analyses indicated that the significant relationship between group and ACE-R ($r=0.326$, $p<0.01$) became non-significant when adjusted for age ($r=0.218$, $p=0.109$), gender ($r=0.297$, $p=0.028$) and education ($r=0.175$, $p=0.200$), thus the differences between groups is related to demographic factors.

Controls did not perform significantly better than depressed participants on the MMSE (Figure 15). Correlations between group and the MMSE were not significant ($p>0.05$) and remained non-significant when adjusted for age, gender and education.

Measure	Depressed	Control	t (df)	z	p value
ACE-R	91.10 (5.8)	94.49 (4.1)	-2.763 (64)		0.011
MMSE	29.00 (1.1)	29.43 (0.8)		-1.623	0.105

Table 20 Mean scores (SD) on the Addenbrooke's Cognitive Examination, Revised and Mini Mental State Examination for depressed and control participants at baseline

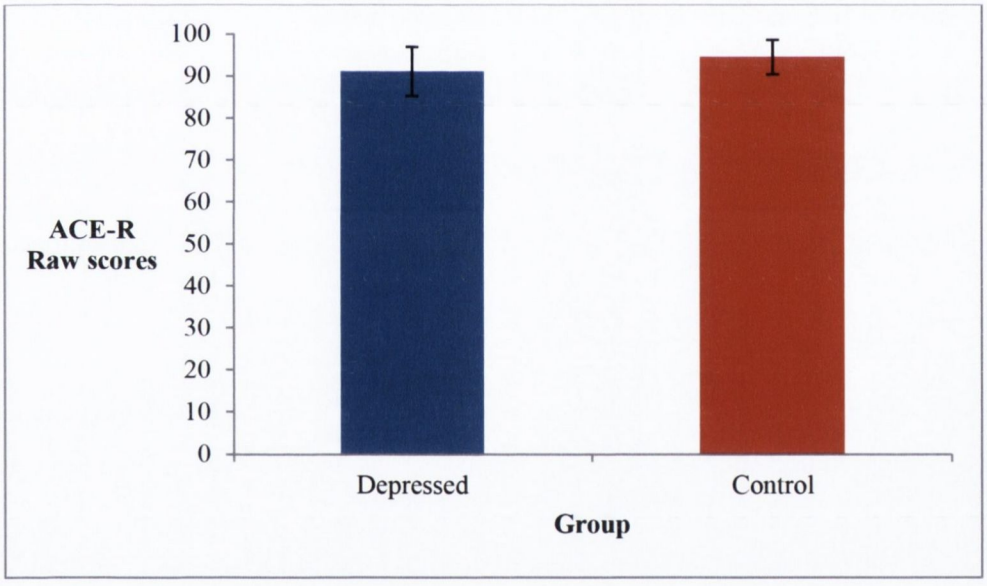


Figure 14 Scores on the Addenbrooke's Cognitive Examination, Revised for depressed and control participants at baseline

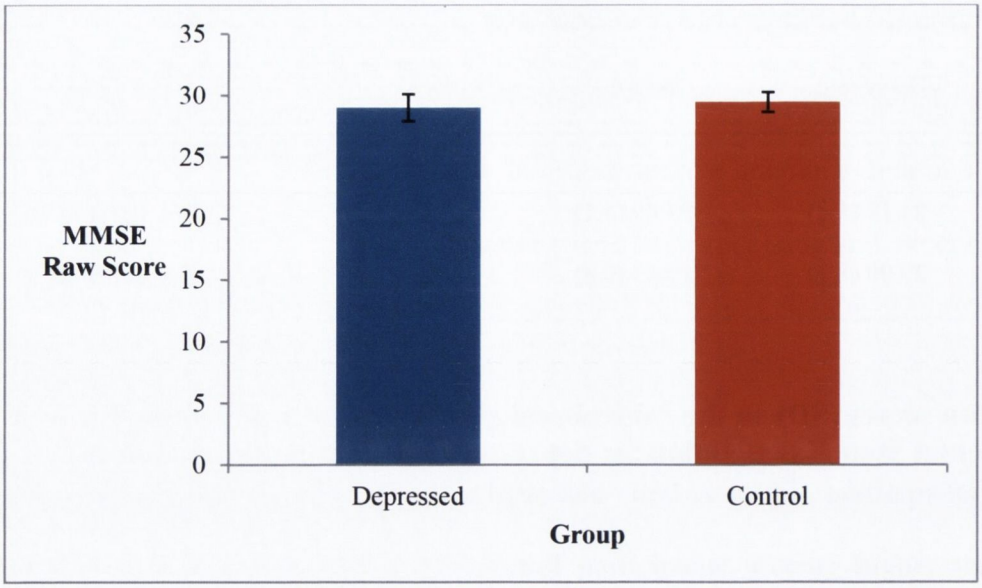


Figure 15 Scores on the Mini Mental State Examination for depressed and control participants at baseline

4.3.1.3.2.2 Retrospective memory

Depressed participants scored significantly lower than control participants on the AMI-SF (Figure 16), indicating worse performance on autobiographical memory recall. In contrast there was no difference between groups for performance on the Public Events Questionnaire at baseline (Figure 17, Table 21).

Similarly a significant relationship was shown between group and AMI-SF performance (rho=0.488, $p<0.001$), which remained significant when age, gender and education were controlled for ($p<0.001$). No significant relationship was found between group and performance on the Public Events Questionnaire for any correlations ($p>0.05$).

Measure	Depressed	Control	t (df)	z	p value
	n=29	n=36			
AMI-SF	49.10 (9.3)	56.38 (3.0)		-3.949	<0.001
Public Events Questionnaire	78.97 (17.3)	77.19 (15.6)	0.433 (63)		0.667

Table 21 Means (SD) for the Autobiographical Memory Interview, Short-form and Public Events Questionnaire for depressed and control participants at baseline

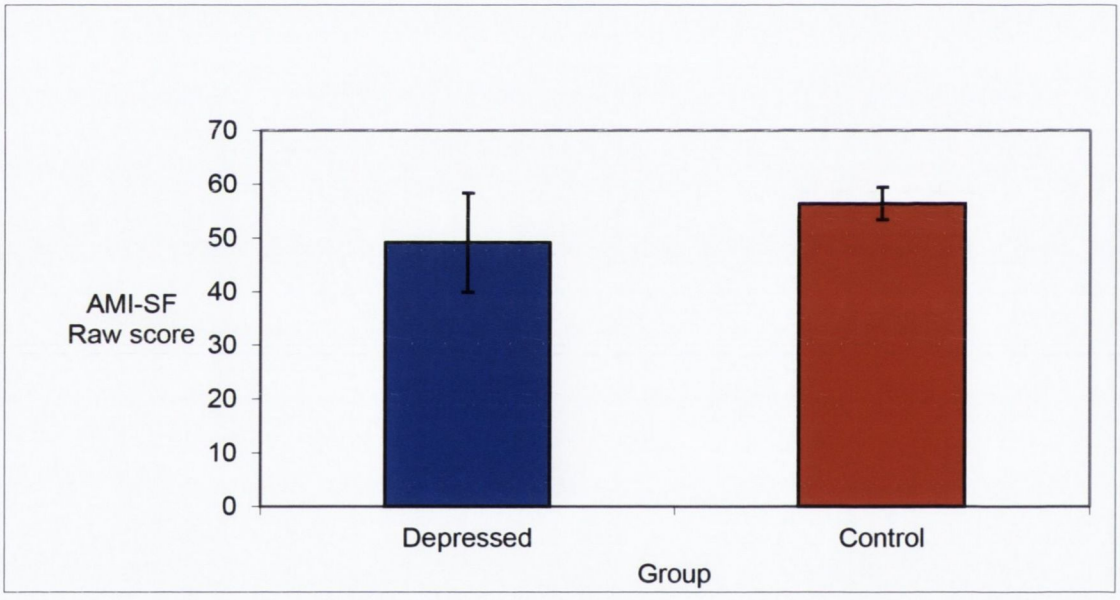


Figure 16 Scores on the Autobiographical Memory Inventory for depressed and control participants at baseline

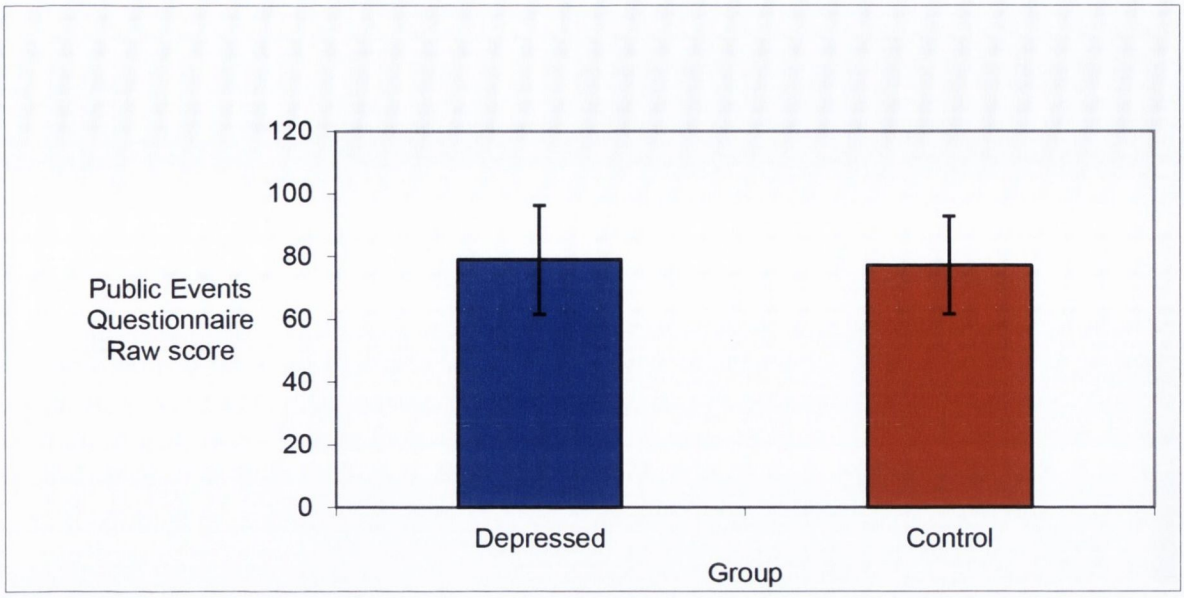


Figure 17 Scores on the Public Events Questionnaire for depressed and control participants at baseline

4.3.1.3.2.4 Anterograde verbal learning and memory

No significant difference was found between depressed and control groups at baseline for total verbal learning (total free recall) on the Buschke FCSR (Figure 18). Similarly no significant difference was found between groups for delayed free recall on the Buschke FCSR (Figure 19, Table 22).

In line with these finding no significant relationships were found between group and total verbal learning or delayed free recall ($p>0.05$). This remained unchanged for both variables when adjusted for age, gender and education ($p>0.05$).

4.3.1.3.2.5 Anterograde visual learning and memory

No significant differences were found between depressed and control participants for ROCF immediate recall (Figure 20) or delayed recall (Figure 21, Table 22). No significant relationships were found between group and ROCF immediate or delayed recall ($p>0.05$). This remained unchanged when age, gender and education were controlled for ($p>0.05$).

Measure	Depressed	Control	t (df)	z	p value
Buschke FCSR					
Total immediate free recall	31.85 (7.1)	33.46 (5.1)		-0.309	0.690
Delayed free recall	12.5 (2.9)	13.32 (2.0)		-1.032	0.302
ROCF					
Immediate recall	18.40 (7.1)	18.93 (6.0)	0.316 (58)		0.753
Delayed recall	17.67 (6.5)	18.64 (6.0)	0.598 (58)		0.552

Table 22 Mean scores (SD) on the Buschke Free and Cued Selective Recall and Rey-Osterrieth Complex Figure for depressed and control participants at baseline

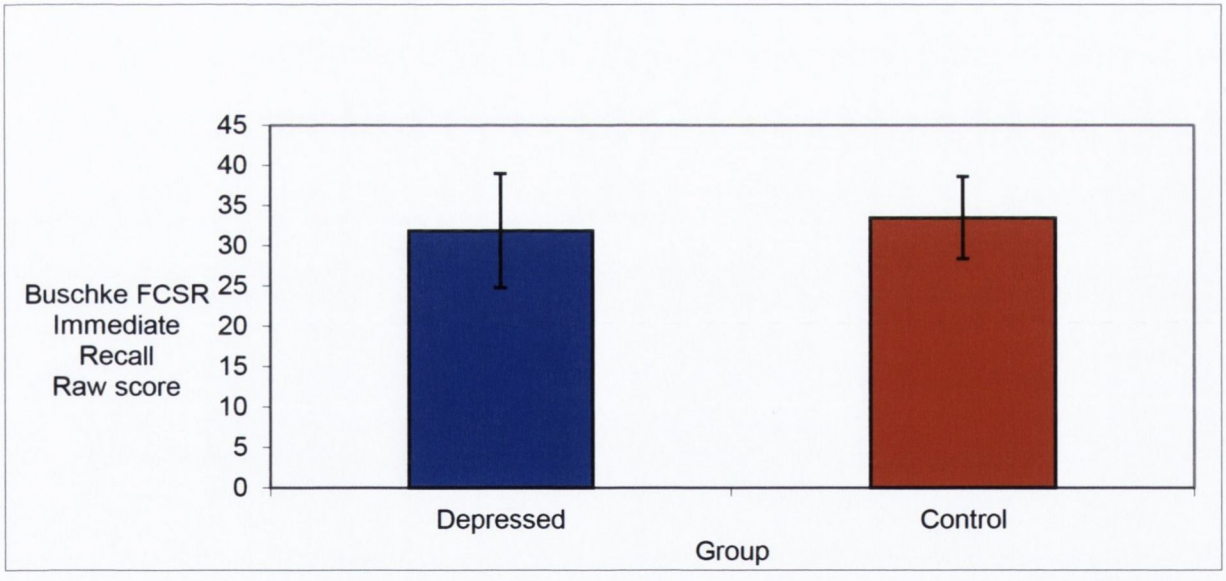


Figure 18 Scores on the Buschke Free and Cued Selective immediate recall task for depressed and control participants at baseline

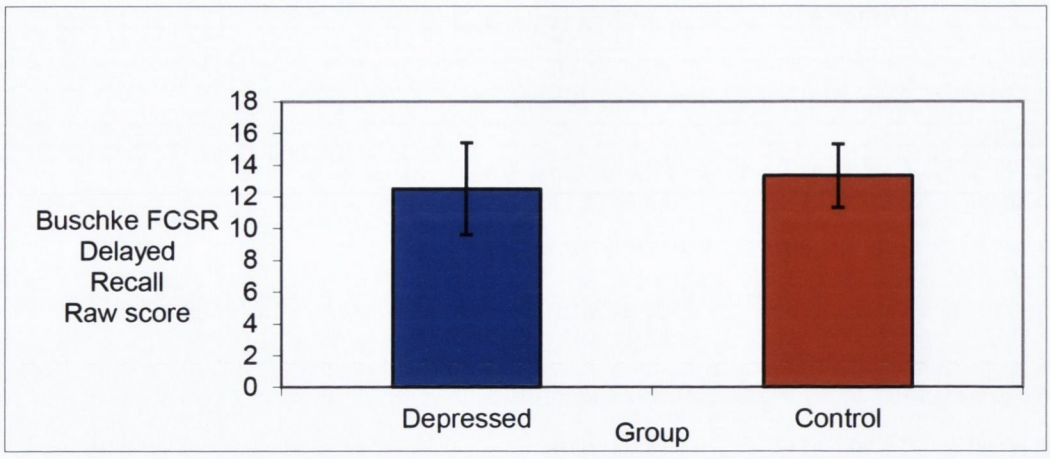


Figure 19 Scores on the Buschke Free and Cued Selective delayed recall task for depressed and control participants at baseline

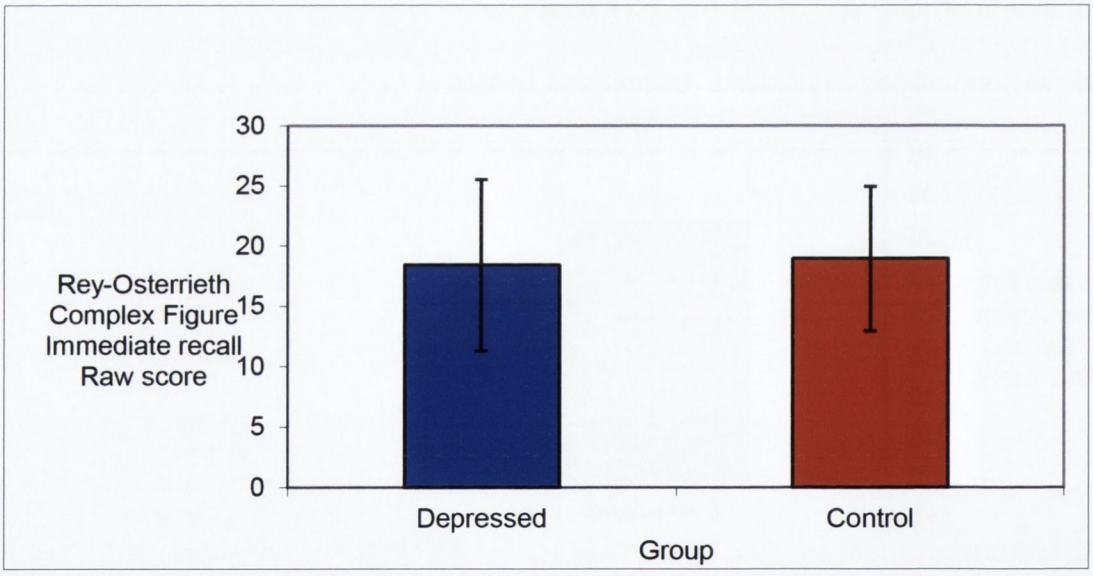


Figure 20 Scores on the Rey-Osterrieth complex figure immediate recall for depressed and control participants at baseline

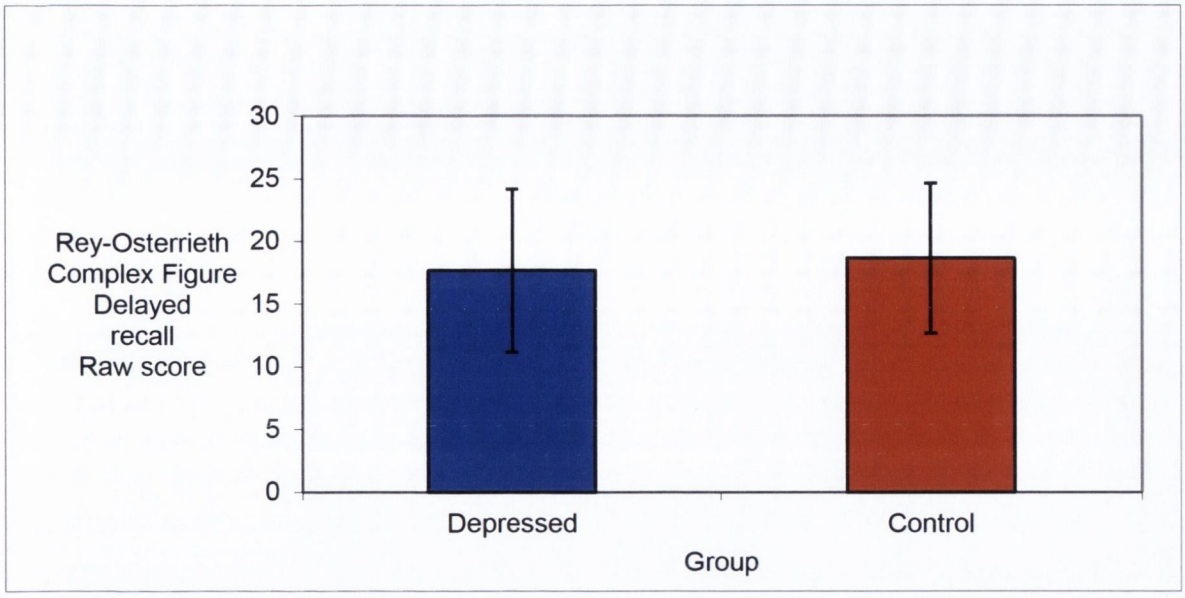


Figure 21 Scores on the Rey-Osterrieth complex figure delayed recall for depressed and control participants at baseline

4.3.1.3.2.7 Attention and working memory

No differences were found between the depressed and control group at baseline for attention as measured by Digit Span Forward (Figure 22) or for working memory as measured by Digit Span Backwards (Figure 23, Table 23).

Similarly, no significant correlations were found between group and Digit Span Forwards or Backwards ($p>0.05$), which remained unchanged when age, gender and education were controlled for ($p>0.05$).

4.3.1.3.2.8 Psychomotor speed and processing

A significant difference was found between depressed and control participants on the Grooved Pegboard Test (Figure 24) where depressed participants took significantly longer to complete the pegboard than controls. The difference between depressed and control participants approached significance for performance on the TMT-A (Figure 25), where depressed participants took longer to complete the test than controls (Table 23).

A significant relationship was found between group and performance on the Grooved Pegboard Test (rho=-0.492, $p<0.001$). This finding remained significant when adjusted for age ($p<0.001$), gender ($p<0.001$) and education ($p<0.001$). A significant relationship was also found for group and performance on the TMT-A (rho=-0.330, $p<0.01$). This finding became non-significant when adjusted for age (rho=-0.306, $p=0.023$) and gender (rho=-0.339, $p=0.011$) although both still approached significance.

Controlling for education did not change the significant relationship between group and the TMT-A (rho=-0.348, $p<0.01$).

Measure	Depressed	Control	z	p value
Digit span forward	9.57 (2.2)	9.73 (2.8)	-0.260	0.794
Digit span backwards	7.41 (1.8)	7.08 (2.9)	-0.918	0.359
Grooved Pegboard Test	86.88 (19.2)	69.69 (11.7)	-3.545	<0.001
TMT-A	39.15 (13.6)	31.05 (9.9)	-2.222	0.026

Table 23 Mean scores (SD) on the Digit span forwards and backwards, the Grooved Pegboard Test and the Trail Making Test Part A for depressed and control participants at baseline

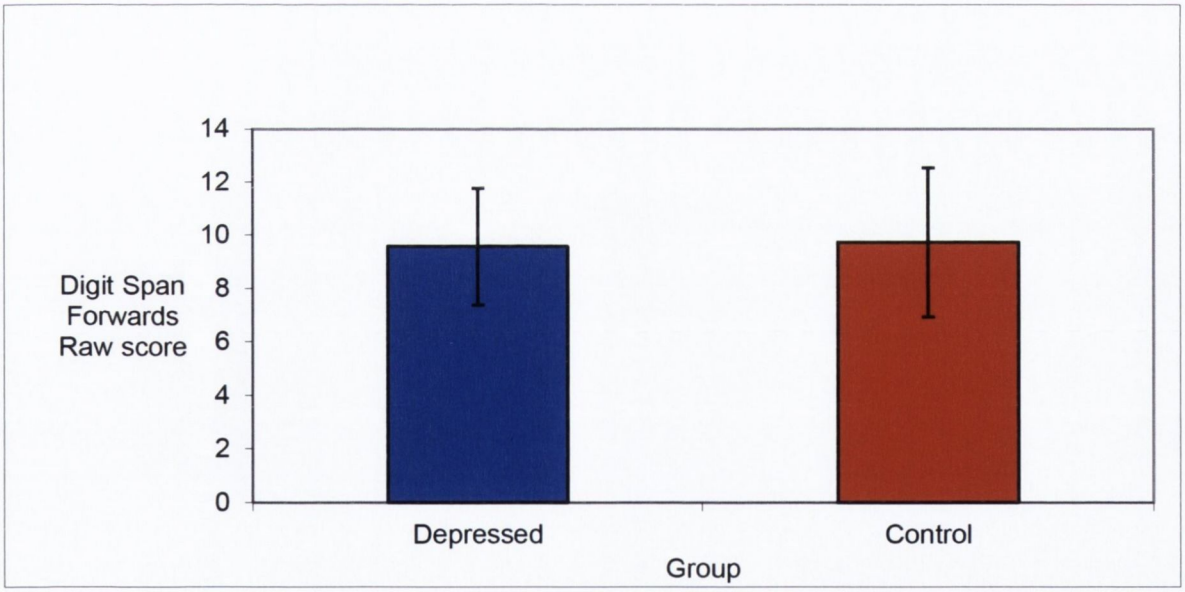


Figure 22 Scores on the Digit span forwards for depressed and control participants at baseline

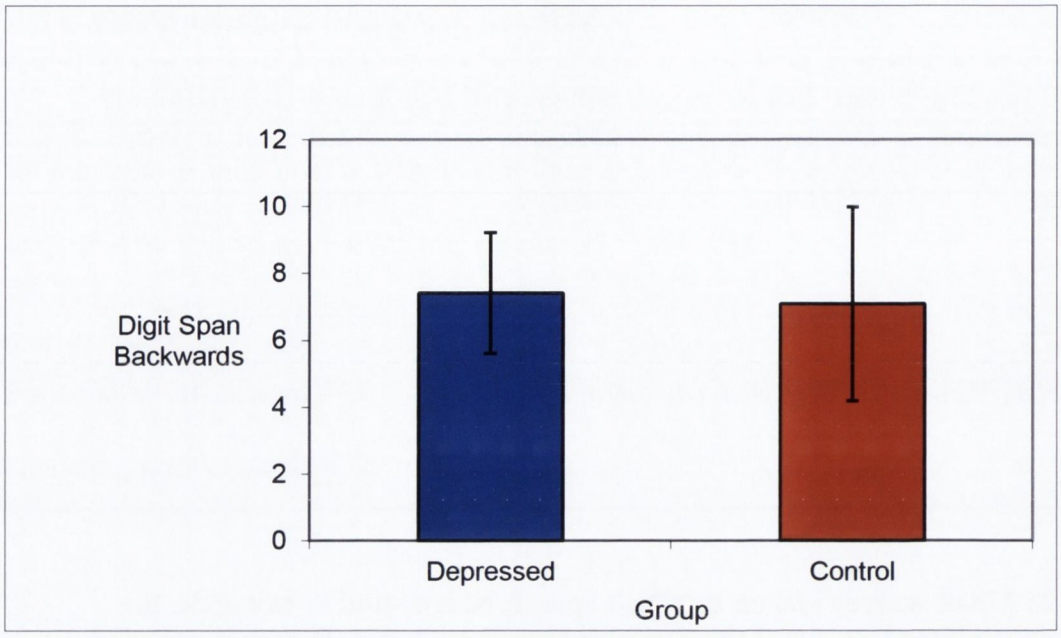


Figure 23 Scores on the Digit Span Backwards for depressed and control participants at baseline

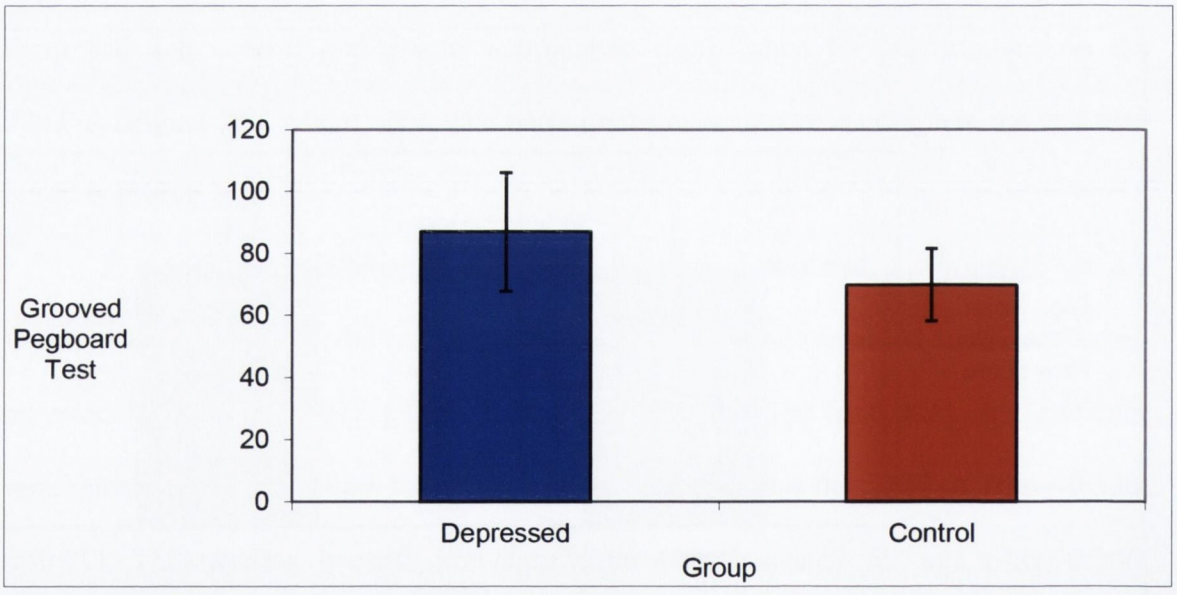


Figure 24 Scores on the Grooved Pegboard Test for depressed and control participants at baseline

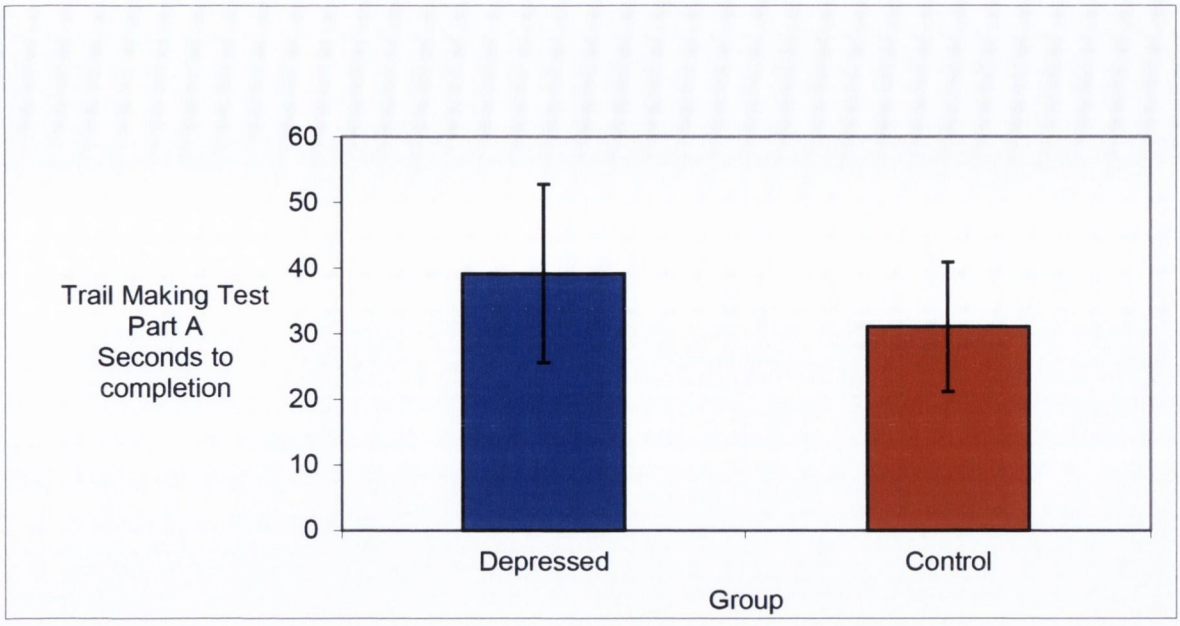


Figure 25 Scores on the Trail Making Test Part A for depressed and control participants at baseline

4.3.1.3.2.9 Executive function

Executive function was measured by performance on fluencies (letter and category) and the TMT-B. Depressed and control participants were comparable on performance on letter fluency (Figure 26), and no significant relationship was found between group and performance on the letter fluency task ($p>0.05$). This remained unchanged when adjusted for age, gender and education ($p>0.05$).

There was a significant difference between groups on category fluency (Figure 27) where depressed participants produced fewer words than controls and a significant relationship was found for group and category fluency ($r=0.349$, $p<0.01$). However, this effect became non-significant when controlling for age ($r=0.182$, $p>0.05$), gender ($r=0.260$, $p>0.05$) and education ($r=0.204$, $p>0.05$), indicating that differences between groups was due to demographic factors rather than depression.

The difference between groups approached, but did not reach significance levels on the TMT-B (Figure 28), with depressed participants taking longer to complete the TMT-B than controls (Table 24). Correlational analyses showed no significant relationship between group and the TMT-B ($p>0.05$), an effect that persisted when age, gender and education were controlled for ($p>0.05$).

Measure	Depressed	Control	t (df)	z	p value
TMT-B	67.38 (24.7)	57.38 (21.6)		-1.984	0.047
Letter fluency	14.86 (5.08)	14.89 (4.8)	-0.024 (64)		0.981
Category fluency	18.79 (4.8)	22.08 (4.2)	2.981 (64)		0.004

Table 24 Mean scores (SD) on the TMT-B, letter and category fluencies for depressed and control participants at baseline

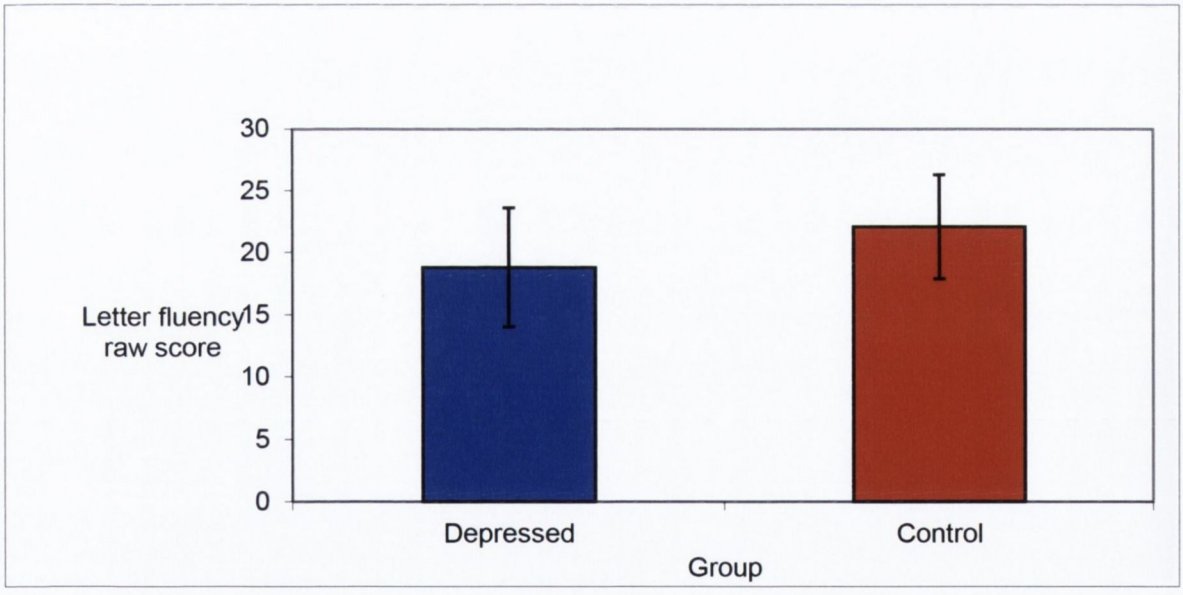


Figure 26 scores on the letter fluency task for depressed and control participants at baseline

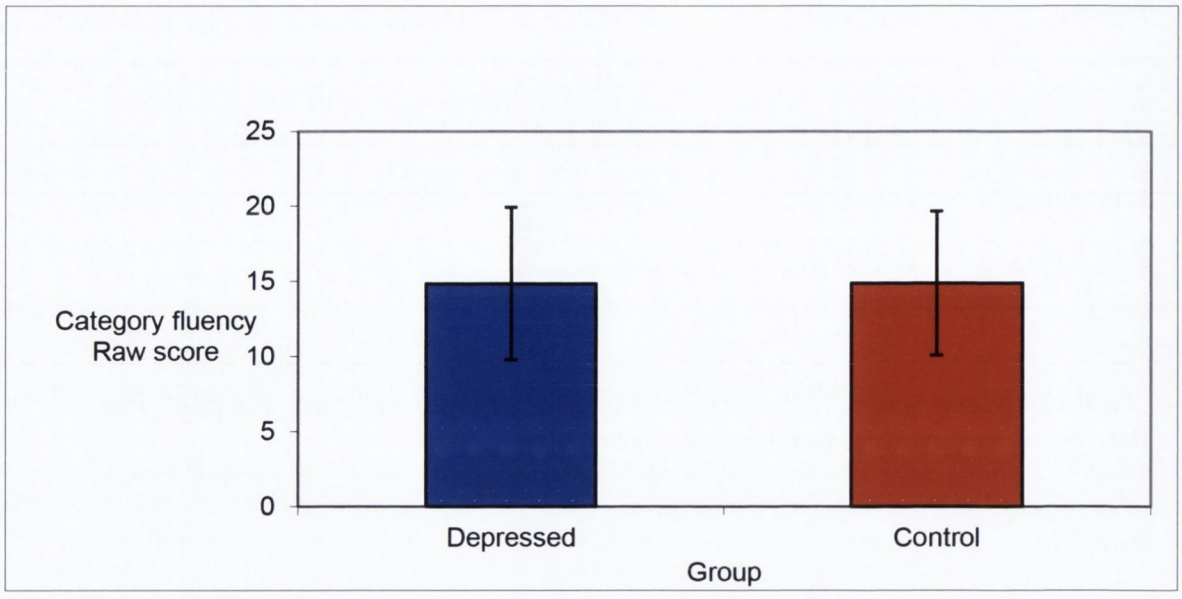


Figure 27 scores on the Category fluency task for depressed and control participants at baseline

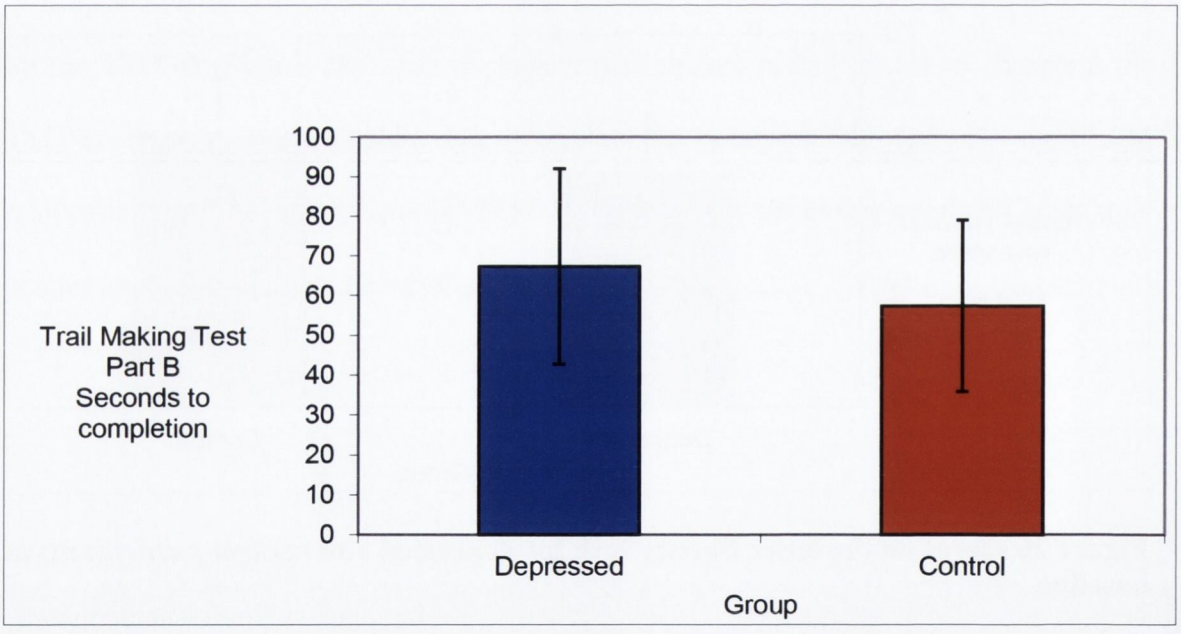


Figure 28 scores on the Trail Making Test B for depressed and control participants at baseline

4.3.1.5 Summary of baseline findings

A group of depressed inpatients who were receiving treatment for a major depressive episode were compared to a group of healthy controls at baseline. Analyses of demographic differences between the groups showed significant differences for age, gender and level of education. No difference was found between groups on the NART.

Analyses of scores on baseline assessments found that the depressed group scored significantly worse on all clinical measures compared to controls. These significant differences remained when baseline differences in age, gender and level of education were controlled for.

The depressed group was found to have impaired performance in some areas of cognition compared to healthy controls. Depressed participants performed significantly worse than controls on the AMI-SF, measuring retrospective autobiographical memory, the Grooved Pegboard Test, measuring psychomotor speed. Differences on category fluency, measuring executive function, were not significant when adjusted for demographic factors. Differences approached significance on the ACE-R, measuring global cognitive impairment, the TMT-A, measuring psychomotor speed and processing and the TMT-B measuring executive function, however none of these remained significant when adjusted for differences in age, sex and education. Thus, the only correlations to remain significant when differences in demographic factors were controlled for were on the AMI-SF and the Grooved Pegboard Test.

4.3.2 Changes with treatment: baseline and two month follow-up comparison in depressed group

From the baseline depressed sample, 22 participants completed follow-up assessments at two months post baseline. Baseline demographic differences between those who completed (completers) and those who did not complete (non-completers) the two month follow-up were assessed using independent t-tests and chi-square analyses. Values are presented in Table 25. No significant differences were found between completers and non-completers for scores on the NART, age in years, level of education and gender.

With regard to differences at baseline between completers and non-completers on clinical and cognitive assessments, no significant differences were found on any measure, although differences on the ACE-R approached significance ($t(27)=2.7$, $p=0.012$), with non-completers performing worse than completers (Table 25).

Measure/characteristic		Completers	Non-completers	Test statistic t (df)	Test statistic $\chi 2$ (df)	p value
		n=22	n=7			
NART- mean (SD)		112.32 (7.5)	111.50 (5.5)	-1.173 (27)		0.251
Age (yrs)- mean (SD)		45.27 (11.7)	51.42 (13.3)	0.545 (23)		0.591
Education level (%)	2nd	7 (31.8)	4 (57)		1.993	0.369
	3rd	12 (54.6)	3 (43)			
	4th	3 (13.6)	0 (0)			
Female (%)		13 (59)	2 (29)		0.947 (1)	0.330
ACE-R- mean (SD)		92.59 (5.1)	86.43 (5.9)	2.700 (27)		0.012
HDRS-24- mean (SD)		29.14 (5.9)	31.00 (6.3)	-0.716 (27)		0.480

Table 25 Baseline characteristics of completers and non-completers of two month follow-up in the depressed group

for National Adult Reading Test, age, education, gender, Addenbrooke's Cognitive Examinaion, Revised and Hamilton Depression Rating Scale, 24 item

4.3.2.2 Clinical and cognitive changes between baseline and two month follow-up

Performance of the 22 depressed participants who completed the two month follow-up assessment was analysed using paired t-tests (t), or Wilcoxin signed ranks tests (z) depending on the normality of the data. The group was not divided into remitted and non-remitted participants as numbers were too low in the remitted group. Instead, relationships between depression severity (score on HDRS-24) and cognitive performance were investigated using Pearson's product moment correlation (r) or Spearman's rho where appropriate. A more stringent significant value of $p<0.01$ was adopted for all analyses to control for effects of multiple testing. In some cases participants did not complete all assessments due to fatigue or time constraint and as such numbers will be lower on some measures than others.

4.3.2.2.1 Clinical changes from baseline to two month follow-up

There was a significant decrease in scoring on the HDRS-24, BPRS and BDI-II at follow-up, indicating less severe depression after treatment (Table 26).

Measure	Baseline	2 month	t (df)	p value
HDRS-24	29.14 (5.9)	18.45 (9.1)	5.161 (21)	<0.001
BPRS	28.67 (4.4)	24.90 (3.9)	3.230 (20)	0.004
BDI-II	30.44 (14.1)	16.28 (8.8)	4.804 (17)	<0.001

Table 26 Baseline and 2 month means (SD) on the Hamilton Depression Rating Scale 24-item, Brief Psychiatric Rating Scale and Beck Depression Inventory-II for depressed participants

4.3.2.2.3 Cognitive changes from baseline to two month follow-up

4.3.2.2.3.1 Global cognitive impairment

No significant differences were found between baseline and two month performance on the ACE-R or the MMSE (Table 27).

Correlations at two months did not find a significant relationship between the HDRS-24 and the ACE-R ($r=-0.305$, $p>0.05$) or the MMSE ($rho=-0.234$, $p>0.05$).

Measure	Baseline	2 month	t (df)	z	p value
ACE-R	92.59 (5.1)	93.6 (5.4)	-0.817 (19)		0.424
MMSE	29.14 (1.0)	29.15 (1.1)		-0.486	0.627

Table 27 Baseline and 2 month means (SD) on the Addenbrooke's Cognitive Examination, Revised and Mini Mental State Examination for depressed participants

4.3.2.2.3.3 Retrospective memory

A significant decrease in AMI-SF scores was found between baseline and two months, though it should be noted that scores at two months were based on percentage consistency with baseline (100%) and thus could not show an increase. A significant improvement was found in scores on the Public Events Questionnaire from baseline to two month follow-up. It should be noted from Chapter 3 that the Public Events Questionnaire is subject to a practice effect, which is likely what is reflected here.

Correlations between scores on the HDRS-24 and the AMI-SF at two months did not show a significant relationship between the two measures ($r=-0.373$, $p>0.05$) but did indicate a moderate correlation between the two, where a higher HDRS-24 score, reflecting more severe depression, was related to a lower AMI-SF score. No relationship was found between performance on the Public Events Questionnaire and the HDRS-24 ($r=0.003$, $p>0.05$, Table 28).

Measure	Baseline	2 month	t (df)	p value
AMI-SF	100 % (0%)	78.64 (11.0)	9.091 (21)	<0.001
Public Events Questionnaire	81.59 (17.6)	86.27 (16.7)	-3.483 (21)	0.002

Table 28 Baseline and 2 month means (SD) on the Autobiographical Memory Interview, Short-form and Public Events Questionnaire for depressed participants

4.3.2.2.3.4 Anterograde verbal learning and memory

No significant difference was found between baseline and two month scores for total verbal learning (total free recall) on the Buschke FCSR. Similarly no significant difference was found between the time-points for delayed free recall on the Buschke FCSR (Table 29).

No significant relationships were found between HDRS-24 and total verbal learning ($r=-0.161$, $p>0.05$) or delayed free recall ($r=-0.360$, $p>0.05$).

4.3.2.2.3.5 Anterograde visual learning and memory

Significant differences were found between baseline and two month performance for ROCF immediate recall and delayed recall with an improvement in performance found for each task (Table 29). Significant negative relationships were found between HDRS-24 and ROCF immediate ($r=-0.538$, $p<0.01$) and delayed recall ($r=-0.596$, $p<0.01$), where a higher score on the HDRS-24 was related to a lower score on the ROCF in both cases.

Measure	Baseline	2 month	t (df)	p value
Buschke FCSR				
Total immediate free recall	33.5 (4.9)	32.25 (6.7)	0.907 (19)	0.376
Delayed free recall	13.15 (2.1)	12.20 (2.7)	1.670 (19)	0.111
ROCF				
Immediate recall	19.03 (6.7)	22.58 (6.3)	-3.339 (18)	0.004
ROCF Delayed recall	18.03 (6.4)	22.58 (6.9)	-4.136 (18)	0.001

Table 29 Baseline and 2 month means (SD) on the Buschke Free and Cued Selective Reminding procedure and Rey-Osterrieth Complex Figure for depressed participants

4.3.2.2.3.7 Attention and working memory

No differences were found between the baseline and two month performance for attention as measured by Digit Span Forward, or for working memory as measured by Digit Span Backwards (Table 30).

No significant correlations were found between HDRS-24 and Digit Span Forwards (rho=0.119, P>0.05) or Backwards (rho=-0.210, p>0.05) at two month assessment.

4.3.2.2.3.8 Psychomotor speed and processing

No significant difference was found between baseline and two month performance on the Grooved Pegboard Test. Similarly there was no significant difference between time-points for performance on the TMT-A (Table 30).

No significant relationship was found between the HDRS-24 and the Grooved Pegboard Test (r=0.191, p>0.05) at two month follow-up. In contrast, the relationship between the HDRS-24 and TMT-A performance at follow-up approached significance (rho=0.493, p=0.027), where participants with a lower score on the HDRS-24 (indicating less severe depression) was related to better performance on the TMT-A.

Measure	Baseline	2 month	t (df)	z	p value
Digit span forward	10.05 (2.7)	9.50 (2.7)		-1.174	0.240
Digit span backwards	7.10 (2.7)	7.80 (3.1)		-1.179	0.239
Grooved Pegboard Test	84.11 (18.3)	82.05 (22.0)	0.967 (18)		0.347
TMT-A	37.70 (14.3)	34.05 (15.3)		-1.429	

Table 30 Baseline and 2 month means (SD) on the Digit Span Forward and Backwards, the Grooved Pegboard Test and the Trail Making Test Part A for depressed participants

4.3.2.2.3.9 Executive function

No significant differences were found between baseline and two month performance on letter fluency or category fluency (Table 31). Similarly no difference between baseline and two month was found for performance on the TMT-B (Table 31).

No significant relationships were found between the HDRS-24 and performance on the letter fluency task ($r=0.146$, $p>0.05$) or category fluency ($r=-0.265$, $p>0.05$). Finally, no significant relationship was found between scores on the HDRS-24 and the TMT-B at two month assessment ($r=0.263$, $p>0.05$).

Measure	Baseline	2 month	t (df)	p value
TMT-B	65.90 (27.1)	65.65 (25.6)	0.044 (19)	0.965
Letter fluency	15.55 (4.9)	16.00 (5.6)	-0.216 (19)	0.831
Category fluency	19.77 (4.4)	20.20 (6.8)	-0.256 (19)	0.801

Table 31 Baseline and 2 month means (SD) on the Trail Making Test Part B and Letter and Category fluency tasks for depressed participants

4.3.2.3 Summary of two month follow-up findings

Participants in the depressed group completed a follow-up assessment at two months post-baseline to measure the effect of treatment in hospital on clinical and cognitive function. In total 22 participants from the original 29 participants in the baseline depressed group completed the follow-up and were included in this analysis.

Baseline differences between those who did and did not complete the follow-up assessment were carried out for all demographic, clinical and cognitive variables. No significant differences were found between completers and non-completers on any measures, although the difference on the ACE-R approached significance, with non-completers performing worse than completers at baseline.

Between baseline and two month follow-up there was a significant drop in scores on all clinical measures (HDRS-24, BPRS and BDI-II), indicating an decrease in depression severity after treatment. With regard to cognitive function performance on the Public Events Questionnaire was significantly improved, however this may be due to a practice effect with the test used. Performance on the ROCF immediate recall and delayed recall also showed a significant improvement from baseline. Further correlational analyses showed a significant relationship between scores on the HDRS-24 and the ROCF immediate and delayed tasks respectively. In contrast scoring on the AMI-SF was significantly lower than baseline. Performance on the AMI-SF was not found to be significantly correlated with scores on the HDRS-24, however evidence of a moderate negative correlation was shown, where higher HDRS-24 scores were linked to lower performance on the AMI-SF. Performance on the Grooved Pegboard Test, on which depressed participants had performed significantly lower than controls at baseline, did not change significantly at two month follow-up. Two month scores on the

Grooved Pegboard Test were also not found to be related to HDRS-24 score at the same time-point. Finally performance on the TMT-A correlated significantly with HDRS-24 scores at two month follow-up.

4.4 Discussion

Baseline analyses of clinical and cognitive functioning were carried out comparing participants with unipolar depression to healthy controls. Findings showed that depressed participants had significantly higher levels of depression and psychiatric symptoms, as measured by the HDRS-24, the BDI-II and the BPRS. Depressed participants also performed at a significantly lower level than healthy controls at baseline on measures of autobiographical memory recall and psychomotor speed. At two month follow-up, depressed participants had significantly lower scores on all clinical measures, as well as on autobiographical memory recall compared to baseline. In contrast, scores had improved significantly from baseline for public events memory however this likely reflects the practice that is found with this instrument (section 3.5.3). Visual learning and memory performance also showed a significant improvement from baseline, however this may have been due to the Taylor figure, used at two month follow-up, begin easier than the Rey-Osterrieth figure used at baseline, as previously reported (section 2.2.1.2).

4.4.1 Clinical findings

The finding that the depressed group had significantly higher scores, indicating more severe depression and psychotic symptoms than the control group, was as expected. Moreover the large difference between groups on the clinical measures reflected the fact that participants in each group were selected based on strict criteria of either having moderate to severe depression, or having no past or present mental health difficulties. The well-defined and distinct nature of each group decreases the likelihood that differences between the groups are due to chance alone. It should also be noted that

depressed participants were included in the study on the basis of having unipolar depression as a primary diagnosis, and no co-morbid diagnoses except in the case of secondary anxiety. This ensured that any effects in the depressed group were due to depression, without any confounding effects of bipolar disorder. In addition, no participant in the depressed group had ever received treatment with electroconvulsive therapy (ECT) prior to taking part in this study, as such avoiding any confounding cognitive difficulties that may have resulted from ECT rather than the depressive illness.

At follow-up assessment there was a significant improvement in depression severity and psychiatric symptoms in the depressed group, however the average HDRS-24 score remained in the moderately depressed range. The impact of depression at two month follow-up on cognition will be will be explored in the following discussion of each set of cognitive functions.

4.4.2 Cognitive findings

Global cognitive function was assessed with the ACE-R which incorporates the MMSE subscale as well as subscales relating to fluencies, visuo-spatial and memory function, language, attention and orientation. At baseline, differences between the groups on the ACE-R approached, but failed to meet, significance at the more stringent significance level employed to correct for multiple testing. These results are similar to a previous study that found participants with MDD to perform at a lower level, though not significantly lower, than healthy controls on the ACE-R (Dudas et al., 2005). However, further investigation of relationships between groups and performance on the ACE-R showed that significant relationships with the ACE-R became non-significant when corrected for age, gender and educational differences, which suggests that the

differences between groups on the ACE-R stemmed from demographic factors rather than depressive symptoms. There was no significant difference between groups on the MMSE, though the depressed group scored slightly lower than controls. One previous study that did find a significant difference between depressed and control groups on the MMSE at baseline assessment, noted that the depressed group still scored in the normal range (Gallassi et al., 2006).

The ACE-R was the only measure to approach significance regarding differences at baseline between completers and non-completers of the follow-up assessment. Within the completers group there was no significant change from baseline on the ACE-R and MMSE. This could suggest a bias in the two month follow-up group, towards those with less cognitive deficits to begin with. However no other cognitive measures were found to be different at baseline between groups of completers and non-completers.

4.4.2.1 Retrospective memory

Assessment of retrospective memory function focused on autobiographical memories and public events memories. Results at baseline showed that autobiographical memory was significantly impaired compared to controls, whereas public events memory was comparable to that of controls. This finding suggests that retrospective memory does not function as one entity, but is dissociable by type of memory. This confirms the results of one earlier study that examined the same functions, but used different assessment scales (Gallassi et al., 2006), thus adding generalisability to these findings.

At two month follow-up the depressed group had significantly improved performance on the Public Events Questionnaire, but significantly lower performance

on the AMI-SF compared to baseline. However these findings must be interpreted in light of the limitations of the assessments used. The Public Events Questionnaire has previously been shown to carry a practice effect (section 3.3.1.4) which corresponds to the increase in scores seen in the depressed group in this part of the study. However, this is still an important finding as it suggests that the depressed group performed in the same manner as controls at two month follow-up, and not at a lower level. In addition, due to the format of the AMI-SF, scored by measuring consistency with baseline performance, participants cannot improve upon baseline performance; they can either match it or perform at a lower level. On average participants failed to recall just over 20% of memories produced at baseline. As no norms are available for consistency of the AMI-SF in a normal population this finding needs to be viewed with caution. This issue will be discussed further in the next chapter, in light of further testing of healthy controls on the AMI-SF.

Despite these limitations the findings are in line with a previous study where depressed participants showed a significant increase in performance on public events memory assessment from baseline to six months follow-up (Gallassi et al., 2006). The same study also found that remitted depressed participants remained impaired on autobiographical memory function at six month follow-up relative to controls. However, assessment of autobiographical memory was carried out by scoring the participants performance on a second administration of the same questionnaire used at baseline, not by measuring consistency with baseline, thus it is not clear as to how many of the original memories were recalled on second administration. In addition, it is not clear if the difference in the interval between initial and baseline assessment may affect performance and thus comparisons of the two month follow-up in the current study to longer follow-ups in other research should be viewed with caution.

Adding to these findings are the results from analyses investigating the relationships between depression severity and retrospective memory at two month follow-up. No relationship was found between mood and public events memory. A moderate, though not significant, relationship was found between depression and autobiographical memory, suggesting that performance on the AMI-SF may be due at least in part to depression, not simply test construction.

4.4.2.2 Anterograde verbal and visual memory

At baseline no differences were found between the depressed and control groups on measures of immediate and delayed verbal and visual memory. This finding contrasts with previous reports of impairment in both visual and verbal memory in depression (Austin et al., 2001, Douglas et al., 2011, Veiel, 1997, Zakzanis et al., 1998), but is similar to one study where no impairments were found in immediate or delayed verbal memory at baseline (Porter et al., 2003). Differences in assessments used to measure verbal memory may have contributed to this effect, and the Buschke FCSR, used in the current study, is designed to promote maximum encoding of verbal material presented.

At follow-up no differences from baseline were detected for performance on immediate and delayed verbal memory. In addition no significant relationship was discerned between verbal memory and depression severity. This is in contrast to recent studies that found verbal learning and memory to be related to depression severity (McDermott and Ebmeier, 2009, Weiland-Fiedler et al., 2004). This may be due to the fact that Buschke parallel versions were not tested for equivalence and as such lack of an improvement could possibly be due to the second version being more difficult.

Performance on immediate and delayed visual memory was however found to have increased significantly from baseline. This is unlikely to have been due to practice

effects as a parallel version of the ROCF were used at each time-point. However, the Taylor figure which was used at the second assessment has been shown to be easier than the original Rey-Osterrieth figure, which was used as baseline (Fastenau et al., 1999) (see section 2.1.3.6). However, significant correlations were also found between both immediate and delayed visual memory and depression severity. Thus it is possible that both improvements in mood and an easier assessment contributed to this effect.

4.4.2.3 Attention and working memory

Attention and working memory were not found to be impaired in depressed participants relative to controls at baseline. Only measures of simple attention were used in the current study, which has been shown not to be affected by depression in previous studies (Veiel, 1997, Zakzanis et al., 1998, Gallassi et al., 2006).

No differences from baseline were found for attention and working memory at follow-up assessment. Other studies that have reported improved performance in remitted participants at follow-up have tended to use more complex, effortful tasks, and as such cannot be usefully compared here. The Gallassi study (Gallassi et al., 2006) reported that remitted depressed participants had improved significantly on digit span forward relative to baseline at six months follow-up, but again this finding must be interpreted with caution in comparison to a two month follow-up, due to difference in the length of time between assessments.

4.4.2.4 Psychomotor speed and processing

Functioning in psychomotor speed and processing was found to be affected in depressed patients compared to controls. This impairment in performance was significant for performance on the Grooved Pegboard Test and approached significance for performance on the TMT-A, although the latter effect did not remain when adjusted

for differences in demographic variables. This finding is in line with previous studies that found evidence of impaired psychomotor speed and processing during a depressive episode (Douglas et al., 2011, Parker et al., 1993).

At follow-up no significant differences from baseline were detected for either the TMT-A or Grooved Pegboard Test, thus suggesting that performance on the Grooved Pegboard Test remained impaired. The TMT-A, but not the Grooved Pegboard Test, was found to be significantly associated with depression score. In this way it is possible that some elements of psychomotor speed and processing are impaired independently of mood, and thus may represent a trait marker for depression, which is somewhat in line with a previous study that found no difference between remitted and non-remitted participants in psychomotor speed at six month follow-up (Gallagher et al., 2007).

4.4.2.5 Executive function

At baseline performance on category fluency was shown to be significantly lower than that of controls, however significant correlations between group and category fluency did not remain when adjusted for age, gender and educational differences. Performance on the TMT-B approached, but did not reach significance levels.

No changes in performance on measures of executive function were found at follow-up, and scores for depressed participants at two months remained below those of controls at baseline. No significant relationships between depression severity and executive function were found at follow-up. As participants in this study remained moderately depressed at follow-up further study is required to disentangle the relationship between executive function and mood following treatment for depression.

4.4.3 Conclusions

Findings of this study, as discussed above, indicate that autobiographical memory and psychomotor speed and processing may be the cognitive functions that are most affected by during a depressive episode. The finding of no significant difference between groups in others areas of cognitive function was somewhat surprising given the clear and significant difference in mood state. While it may be the case that these functions are not affected by depressed mood, it is also important to consider other factors such as: were the assessments used suitable to capture and demonstrate weaker performance in a depressed population?; was the current sample better educated and younger than those described in other studies?

At two month follow-up reduced performance may persist in autobiographical memory and psychomotor speed and processing. Performance in some cognitive domains was found to be associated with severity of depression, however a clear state or trait relationship is difficult to ascertain as the depressed group on average remained moderately depressed at 2 month follow-up.

4.4.4 Limitations, strengths and future directions

While results of the above studies were broadly in line with previous findings, the small number of participants in each group limits the power to detect true differences between groups. The small sample size in the depressed group was a side-effect of maintaining a pure sample of unipolar depressed participants with no previous ECT. In addition, as participants were recruited for the purposes of participating in the longitudinal Mem-Dep Study, requiring assessment over the course of one year, participants in both groups may have been put off by the level of commitment involved in taking part in the study.

Secondly, some of the measures used in the assessment battery may have also limited these findings. For example, only simple attention was measured here, which in the past has been shown to not be affected by depression (Veiel, 1997, Zakzanis et al., 1998). It is possible that differences between groups may have been shown if measures of sustained or divided attention were employed instead, such as the Sustained Attention Response Task (Robertson et al., 1997). Similarly, the use of the Buschke FCSR may have masked any effects of depression, by promoting a high level of encoding of the verbal material. However, this could also be interpreted as a strength of the measure, because by controlling for poor encoding any differences in performance can then be attributed to deficits in recall with more certainty. Similarly, the AMI-SF and Public Events Questionnaire have their limitations as measures of autobiographical memory and public events memory; however as measures of consistency of retrospective memory they are suitable for the measurement of retrospective memory over time, as seen in the study of performance at two month follow-up and as discussed further in the following chapters.

The assessment of change in cognitive function at two month follow-up was not as informative as had been hoped, given that a large number of participants remained moderately depressed at this time-point. It is unclear as to why so many of the sample remained depressed at this time-point, as the effect of antidepressant medication would usually be seen within three to four weeks of treatment. It is possible that the current sample, due to small numbers, is not representative of normal response to treatment.

Despite these limitations this study has added to the knowledge of cognitive functioning in depression, in a group of unipolar depressed participants, who, unlike many previous studies, had no previous treatment with ECT. The study also adds to the

sparse findings regarding the functioning of retrospective memory in depression, and has provided important information regarding the consistency of retrospective memories over time during a depressive episode. Specifically, the finding that autobiographical memory functioning is affected by depression, whereas public events memory is not, provides more evidence for fractionation of long term memory. In addition, this finding is of great importance when related to studies carried out in the area of ECT, in that the current findings suggest that autobiographical memory is likely to be affected by depression itself, and post-ECT findings of impairment in autobiographical memory may in fact be explained in part by depressed mood.

It would be desirable to see these findings repeated with a larger group of both depressed and control participants in future. In addition, there is a need for longer term follow-up assessments in depression, to investigate any further changes, or lack thereof, in both clinical and cognitive outcomes. It is also important to include a long-term control group, to ensure any changes in cognitive functioning are due to the change in depressive severity and are not simply due to the passage of time. In the next chapter this is investigated by examining change in performance of a depressed and control group at six and twelve months after baseline.

CHAPTER 5: RETROSPECTIVE MEMORY AND GENERAL COGNITION IN DEPRESSED AND CONTROL PARTICIPANTS AT SIX AND 12 MONTH FOLLOW-UP

5.1 Introduction

In recent years there has been increased interest in the longitudinal effects of depression on cognition (Biringer et al., 2007, Douglas and Porter, 2009); however studies of more than six month follow-up from baseline are rare. In addition, many studies of cognitive function in the remitted phase of depression are conducted by comparing euthymic depressed patients and controls on a single occasion only (Paelecke-Habermann et al., 2005, Paradiso et al., 1997, Weiland-Fiedler et al., 2004), therefore missing out crucial information regarding any changes in functioning between the acute phase of the depressive episode and the current assessment time-point. Compounding the problem further is the fact that most studies are still lacking in a healthy control group that is followed up at the same time-points as the depressed group. This is important for longitudinal studies as the effects that passage of time may have on performance, both in depressed groups and healthy controls, need to be taken into account (McDermott and Ebmeier, 2009). One recent study assessed a group of depressed patients at baseline and two year follow-up and found improvements in attentional function compared to performance at baseline, and improvements in verbal memory to the level of healthy controls at baseline (Biringer et al., 2007). This highlights how cognition may change over time; however, the same study did not re-test controls at follow-up. Therefore changes due simply to passage of time are not accounted for. Most other published studies only follow-up participants from baseline

to six months or less (Beblo et al., 1999, Gallassi et al., 2006). There is thus a need for longer-term follow-up with both depressed and healthy control participants to disentangle the effects of time and acute depression, as well as recovery from depression, on cognitive functioning.

Studies of cognitive functioning in depression have also tended to avoid studying retrospective memory functions, such as autobiographical and public events memory. Where studies have examined autobiographical memory in depression, they have usually concentrated solely on the phenomenon of overgeneral memory recall (Williams, 1988, Williams et al., 2007) and in the absence of assessment of any other cognitive functions. Furthermore, the consistency of retrospective memory recall has, to the best of my knowledge, never been systematically examined in the context of depression, and where data do exist they relate to small groups of psychiatric controls in older studies mainly involving electroconvulsive therapy (ECT) (Calev et al., 1989, Squire et al., 1981).

This section of The Mem-Dep Study, examining retrospective memory and general cognition in depression, aimed to address some of these issues by assessing differences between depressed participants and healthy controls at three time-points over a one year follow-up, where controls are tested and re-tested at the same intervals as depressed participants. In addition two retrospective memory functions were assessed, namely autobiographical memory and public events memory, in addition to a comprehensive assessment battery covering anterograde verbal and visual learning and memory, attention, psychomotor speed and processing and executive function.

The hypotheses being tested in this part of the study were:

- At 12 month follow-up retrospective memory function and cognition would be at the same level as controls in patients who remit and remain well.

- Performance on measures of retrospective memory and general cognitive function would improve over time as depression severity decreases.

5.2 Methods

5.2.1 Ethics and Consent

Full ethical approval was granted for this study by the St. Patrick's University Hospital Research Ethics Committee (Protocol number 01/08 – Appendix 19) and the Trinity College Dublin, School of Medicine, Faculty of Health Sciences Research Ethics Committee (Appendix 20).

5.2.2 Design

This part of the Mem-Dep study had a case-control repeated measures design, investigating retrospective memory function and other cognitive function over a 12 month follow-up period in depressed participants and healthy controls. The study had two independent variables - group (depressed or control) and time (baseline, six month follow-up and 12 month follow-up). The main dependent variables were autobiographical and public events retrospective memory, measured by the Autobiographical Memory Inventory Short-form (AMI-SF) (McElhiney et al., 1997, McElhiney et al., 1995) and the Public Events Questionnaire respectively.

5.2.3 Participants

Participants in the depressed group were patients ≥18 years admitted to St. Patrick's University Hospital or St. Edmundsbury Hospital with unipolar major depressive disorder (diagnosis confirmed using Structured Clinical Interview for

Diagnostic and Statistical Manual (DSM) (American Psychiatric Association, 2000), Axis 1 (SCID-1) (First et al., 1995) and a Hamilton Depression Rating Scale 24-item (HDRS-24) (Hamilton, 1960, Kovacs et al., 1981) score of ≥ 21. Participants could not have a co-morbid psychiatric diagnosis, except where anxiety was diagnosed secondary to major depressive disorder. All participants required English as their first language. Exclusion criteria comprised diagnosis of dementia or other Axis 1 diagnosis; alcohol/other substance abuse in previous six months; past history of treatment with electroconvulsive therapy (ECT); major sensory deficit; inability/refusal to consent.

Participants in the control group were aged ≥ 18; had English as first language; had a HDRS-24 score of ≤8 and Mini Mental State Examination (MMSE) ≥26 (Folstein et al., 1975). Controls were excluded from participation if they had any past psychiatric history; previous ECT; current major medical illness/major sensory deficit; alcohol/other substance abuse in previous six months; or inability/refusal to consent.

Participants in both groups in this section of The MEM-Dep Study were drawn from the same pool as the baseline participants described in Chapter 4 (section 4.2.2), and were included in this section based on a complete case analysis, i.e., all those that completed all three assessments were included in the follow-up study.

5.2.4 Procedure

Once consenting participants met relevant inclusion and exclusion criteria the neuropsychological testing was carried out. The complete assessment battery was carried out at all assessments where possible. Baseline assessment of depressed participants was carried out as soon as suitable participants were identified following admission to hospital. Depressed and control participants were followed up at six and

12 months after the initial assessment, as outlined in Table 32. Standardised neuropsychological and clinical assessments were used where possible and many tests were chosen for comparability to those used in other similar published studies. Testing took approximately two hours to complete and the researcher was present at all times and guided participants through all assessments.

Assessment	baseline		2 month follow-up		6 month follow-up		12 month follow-up	
	Patient	Control	Patient	Control	Patient	Control	Patient	Control
HDRS[24]	✓	✓	✓		✓	✓	✓	✓
SCID-I	✓	✓						
Treatment Review	✓	✓	✓		✓	✓	✓	✓
ATHF	✓							
NART	✓	✓						
BPRS	✓	✓	✓		✓	✓	✓	✓
AMI-SF	✓	✓	✓		✓	✓	✓	✓
Public Events Questionnaire	✓	✓	✓		✓	✓	✓	✓
ACE-R	A	A	B		C	B	D	C
Digit span	I	I	II		III	II	I	III
Buschke FCSR	1	1	2		3	2	1	3
ROCF	A	A	B		C	B	D	C
Trail Making Test	✓	✓	✓		✓	✓	✓	✓
Grooved Pegboard Test	✓	✓	✓		✓	✓	✓	✓
BDI-II	✓	✓	✓		✓	✓	✓	✓

Table 32 Schedule and list of The Mem-Dep Study assessments

ATHF: Antidepressant Treatment History Form; SCID-I: Structured Clinical Interview DSM-IV, Axis 1; HDRS-24: Hamilton Depression Rating Scale; BDI-II: Beck Depression Inventory II; BPRS: Brief Psychiatric Rating Scale; NART: National Adult Reading Test; ACE-R: Addenbrooke's Cognitive Examination, revised (Parallel versions A,B,C,D); AMI-SF: Autobiographical Memory Interview, Short-form; Buschke Free and Cued Selective Reminding (FCSR) with parallel versions 1, 2 and 3; ROCF: Rey-Osterrieth Complex Figure with parallel versions A, B, C, D; Digit Span (Forwards and backwards) with parallel versions I, II and III; TMT-A: Trail Making Test Part A; and TMT-B: Trail Making Test Part B.

5.2.6 Data analyses

Data analyses were based on complete case analysis, whereby only data from participants who had completed assessments at all time-points were included. Results are presented as mean (M) and standard deviation (SD). Independent t-tests (t), or Mann Whitney U tests (z) as the non-parametric alternative, were used to identify any baseline differences between completers and non-completers of all assessments. Independent t-tests were also used to identify any demographic differences at baseline between depressed and control participants included in this arm of the study. Non-parametric alternatives were used where data were not normally distributed. Cognitive measures that assessed the same cognitive function could be assessed using multivariate ANOVA's, once test assumptions were met. Where assumptions for multivariate analyses were not met data were instead analysed using univariate ANOVA's and the p value was adjusted for multiple comparisons (Pallant, 2007). Longitudinal data were analysed using mixed between-within ANOVA's with Bonferroni post-hoc tests. This type of ANOVA examines main effects where one independent variable is between groups (i.e. participant group, depressed or control), and one independent variable is within groups (time of assessment) (Shaughnessy et al., 2003). Where significant effects were found within groups additional one-way repeated measures ANOVA's were conducted to find where the differences lay within each group. Where significant differences were found between groups independent t-tests (or non-parametric alternatives) were used to assess which time-periods the differences lay between. Effect-sizes were estimated using partial eta-squared, as recommended for mixed between-within ANOVA's (Shaughnessy et al., 2003, Pallant, 2007). Partial eta-squared explains the proportion of the variance in the dependent measure that is attributable to

the independent variable. All data were analysed using SPSS version 16 (SPSS Inc., 2009).

5.3 Results

From the baseline depressed sample, 15 depressed and 21 control participants completed follow-up assessments at baseline, six and 12 month time-points. Of the depressed participants who returned for follow-up some had completed the additional two month assessment reported in the previous chapter. To investigate any potential practice effects within those participants, arising from the extra assessment point, changes in their performance between two and six month follow-up were analysed using paired t-tests. There were no significant changes in performance for this group from two to six month follow-up, although the decrease in scores on the AMI-SF approached significance ($p=0.025$). This will be taken into account in the discussion of the longitudinal analyses presented here.

Baseline demographic differences between those who completed (completers) and those who did not complete (non-completers) the six and 12 month follow-ups were assessed using independent t-tests and chi-square analyses (see Table 33). No significant differences were found at baseline between completers and non-completers in the depressed group for scores on the National Adult Reading Test (NART, (Nelson and Willison, 1991)) age (in years), level of education and gender. Similarly, no differences were found between completers and non-completers at baseline in the control group on the NART, age (in years), level of education and gender (Table 33).

No significant differences were found between completers and non-completers on any cognitive measure at baseline except for Digit Span Forward in the depressed

group, where non-completers scored significantly higher than completers. There were no differences in baseline HDRS-24 scores between completers and non-completers in the depressed group (Table 33).

Changes to medications over the one year follow-up are documented in Table 34. Due to the possible effects of benzodiazepines and TCAs on memory function, the number of participants taking each medication was recorded. A number of participants in the depressed group were taking benzodiazepines during this study, specifically, five at baseline, three at six months and five at twelve month follow-up. In addition, one participant was taking TCA's at baseline, and remained on them at six and twelve months.

Measure/characteristic		Completer	Non-completer	Test Statistic		
				t (df)	χ2 (df)	p
Depressed Group		*n=15*	*n=14*			
NART, mean (SD)		113.15 (7.4)	112.58 (6.9)	0.199 (23)		0.844
Age, years (SD)		47.60 (13.7)	45.86 (10.7)	0.379 (27)		0.705
Education, level (%)	2nd	6 (40)	5 (36)			
	3rd	7 (47)	8 (57)		0.457 (2)	0.793
	4th	2 (13)	1 (7)			
Female, n (%)		9 (60)	6 (43)		0.304 (1)	0.581
Digit Span Forward, mean (SD)		8.31 (6.5)	11.15 (2.1)	-2.777 (z)		0.005
HDRS-24, mean (SD)		30.87 (6.5)	28.21 (5.1)	1.210 (27)		0.237
Control Group		*n=21*	*n=16*			
NART, mean (SD)		112.48 (6.2)	112.63 (5.5)	-0.078 (35)		0.940
Age, years (SD)		42.95 (14.8)	34.69 (10.8)	1.965 (35)		0.057
Education, level (%)	2nd	3 (14)	1 (6)			
	3rd	12 (57)	11 (69)		0.782 (2)	0.676
	4th	6 (29)	4 (25)			
Female, n (%)		17 (81)	12 (75)		0.001 (1)	0.974

Table 33 Baseline characteristics of completers and non-completers of six and 12 month follow-ups

	Baseline	6 month	12 month
SSRI	8	6	5
SNRI	6	4	4
TCA	1	1	1
NaSSA	3	2	2
Benzodiazepine	5	3	5
Lithium	1	3	2
Anticonvulsant	1	3	3
Antipsychotic	4	3	3
Non-benzodiazepine hypnotic	7	5	4

Table 34 Medication change over time in depressed participants

SSRI: Selective Serotonin Re-uptake Inhibitors; SNRI: Serotonin Noradrenaline Re-uptake Inhibitor; TCA: Tricyclic Antidepressant; NaSSA: Noradrenergic and Specific Serotonergic Antidepressants

Baseline differences were also assessed between completers in the depressed and control groups. No differences were found at baseline between depressed and control participants on the NART, age (in years), level of education and gender (Table 35).

Measure/ characteristic		Depressed	Control	Test statistic		
				t (df)	χ2 (df)	p
		n=15	*n=21*			
NART, mean (SD)		113.15 (7.4)	112.48 (6.2)	0.288 (32)		0.775
Age (years), mean (SD)		47.60 (13.7)	42.95 (14.8)	0.959 (34)		0.345
Education, level (%)	2nd	6 (40)	3 (14)		4.679 (2)	
	3rd	7 (47)	12 (57)			0.179
	4th	2 (13)	6 (29)			
Female, n (%)		9 (60)	17 (81)		1.103 (1)	0.314

Table 35 Baseline characteristics of depressed and control groups who completed 6 and 12 month follow-up

5.3.2 Clinical and cognitive changes from baseline over one year follow-up

Performance of the 15 depressed and 21 control participants who completed baseline (baseline), six month (six months) and 12 month (12 months) follow-up assessments was analysed using mixed plot ANOVA's, examining main effects within groups over time, between groups and the interaction between time and group. While multivariate analyses would be most suitable to analyse these data, analyses of cognitive measures grouped by type of cognitive function showed that the data did not meet the assumptions of normality, multicollinearity and singularity necessary for multivariate analyses. For this reason univariate analyses, where each assessment measure was analysed separately, were conducted for all measures and a more stringent significance value of $p<0.01$ was adopted for all analyses to control for effects of multiple testing. Further tests were conducted where significant differences were found within and between groups, using repeated measures ANOVA and independent t-tests respectively, to pinpoint where the differences arose. Effect-sizes were estimated using partial eta-squared to indicate the proportion of the variance in the dependent measure that was attributable to the independent variable.

5.3.2.1 Clinical changes over one year follow-up

A significant interaction between group and time was found for the HDRS-24 (Table 36). A significant main effect of group was found on the HDRS-24, with depressed participants scoring significantly higher than controls. Post-hoc analyses indicated that this effect was significant between groups for all time-points ($p<0.001$). A significant difference was also found within groups over time on the HDRS-24. Further

analyses (one-way repeated measures ANOVA) indicated that difference in HDRS-24 scores were significant between baseline and six months and baseline and 12 months for the depressed group. There was no significant difference between HDRS-24 scores at six months and 12 months ($p>0.05$) for depressed participants. Scores on the HDRS-24 in the control group did not change significantly over time (Table 36, Figure 29).

Measure	Time	Depressed group n=15	Control group n=21	Comparison	F (df)	p value	Effect-size
HDRS-24	Baseline	30.87 (6.5)	2.86 (2.3)	Group	111.076 (1)	<0.001	0.766
	Six month	18.73 (10.5)	4.05 (2.8)	Time	15.243 (2)	<0.001	0.480
	12 month	16.47 (11.47)	3.19 (2.7)	Group*time	18.003 (2)	<0.001	0.522

Table 36: Change in Hamilton Depression Rating Scale (24 item) scores over one year follow-up. Data are presented as mean (SD).

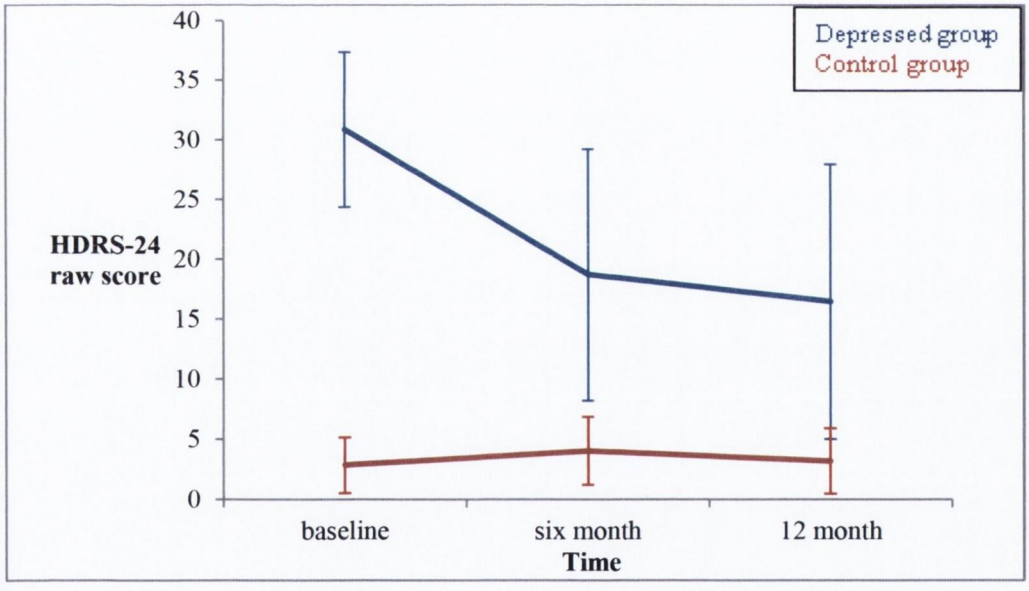


Figure 29 Hamilton Depression Rating Scale (24 item) scores over one year follow-up

A significant interaction between group and time was also found for the BDI-II (Table 37, Figure 30). A significant main effect of group was also found on the BDI-II, with depressed participants rating themselves as significantly more depressed than controls. Post-hoc analyses indicated that this effect was significant between groups at baseline and six months ($P<0.01$) but not at 12 months ($p=0.032$). A significant difference was also found within groups over time on the BDI-II (Table 37). Further analyses (one-way repeated measures ANOVA) indicated that the differences were within the depressed group only and were significant between baseline and six months, and baseline and 12 months. There was no significant difference between scores at six months and 12 months ($p>0.01$) for depressed participants.

No significant interaction was found between group and time on the BPRS. A significant main effect of group was found on the BPRS, again with depressed participants scoring significantly higher than controls. Post-hoc analyses indicated that this effects was significant between groups for all time-points ($p<0.001$). No significant difference was found within groups over time on the BPRS (Table 38, Figure 31), although the difference approached significance.

Measure	Time	Depressed group n=11	Control group n=21	Comparison	F (df)	p value	Effect-Size
BDI-II	Baseline	35.00 (13.4)	1.81 (2.0)	Group	58.154(1)	<0.001	0.660
	Six month	17.45 (14.9)	2.00 (2.8)	Time	27.129 (2)	<0.001	0.652
	12 month	13.55 (14.8)	2.38 (3.2)	Group*Time	29.460 (2)	<0.001	0.670

Table 37 BDI-II means (SD) over one year follow-up

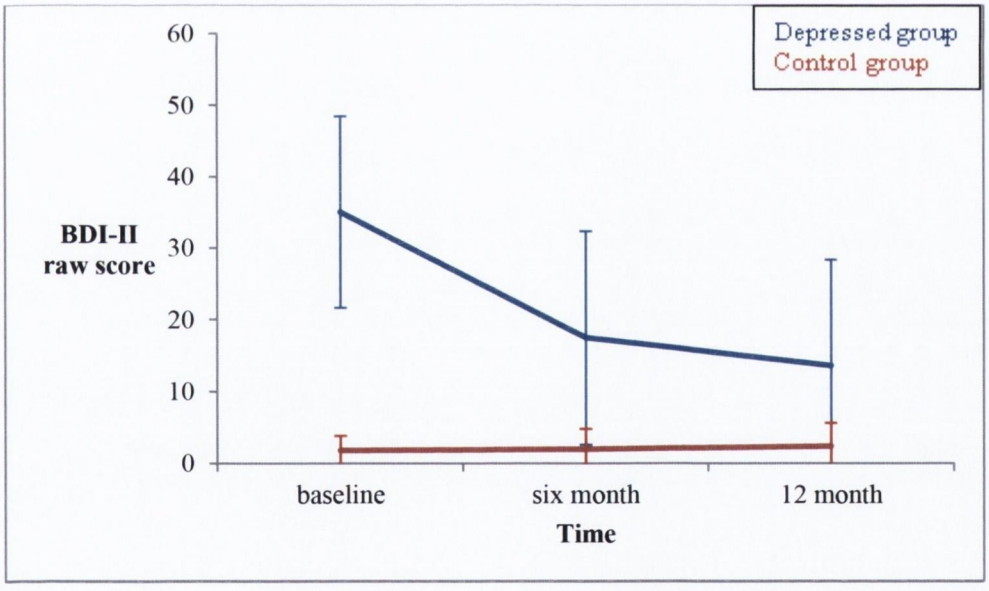


Figure 30 BDI-II means (SD) over one year follow-up

Measure	Time	Depressed Group n=10	Control Group n=21	Comparison	F (df)	p value	Effect-Size
BPRS	Baseline	28.00 (4.6)	19.09 (1.2)	Group	4.5899 (1)	<0.001	0.670
	Six month	24.80 (5.1)	18.95 (1.0)	Time	5.251 (2)	0.012	0.273
	12 month	23.30 (5.4)	18.95 (1.1)	Group*Time	4.726 (2)	0.017	0.252

Table 38 Brief Psychiatric Rating Scale means (SD) over one year follow-up

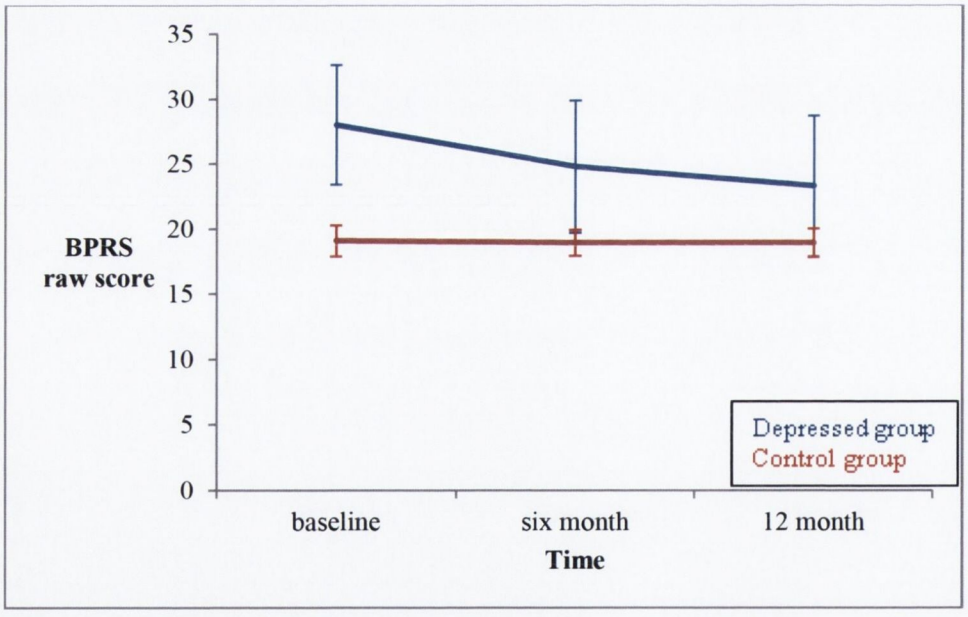


Figure 31 Brief Psychiatric Rating Scale means (SD) at over one year follow-up

5.3.2.2 Summary of clinical findings

Clinical measures of depressive symptoms were significantly higher in the depressed group than the control group at all times, except for the BDI-II at 12 month follow-up. At 12 months on the BDI-II there was no significant difference between groups, although depressed participants still had a higher score on average than controls. Over time the control group had no significant change in scores on clinical measures. In contrast the depressed group had significantly lower scores on the HDRS-24 and BPRS between baseline and six month and baseline and 12 month assessments. The depressed group showed no further significant decrease in scores on these measures between six and 12 month follow-up.

5.3.2.3 Cognitive changes over one year follow-up

5.3.2.3.1 Global cognitive impairment

No significant interaction was found for performance on the ACE-R over six and 12 month follow-up from baseline between group and time. No significant difference was found between groups or within groups over time (Table 39, Figure 32).

No significant interaction was found between group and time on the MMSE. No significant differences were found on the MMSE between groups or over time (Table 40, Figure 33).

Measure	Time	Depressed group n=11	Control group n=21	Comparison	F (df)	p value	Effect-Size
ACE-R	Baseline	92.73 (4.5)	93.43 (4.7)	Group	00.317 (1)	0.577	0.010
	Six month	92.73 (5.4)	94.14 (5.2)	Time	0.753 (2)	0.480	0.049
	12 month	93.64 (3.8)	94.29 (5.0)	Group*Time	0.226 (2)	0.799	0.015

Table 39 Addenbrooke's Cognitive Examination-Revised means (SD) over one year follow-up

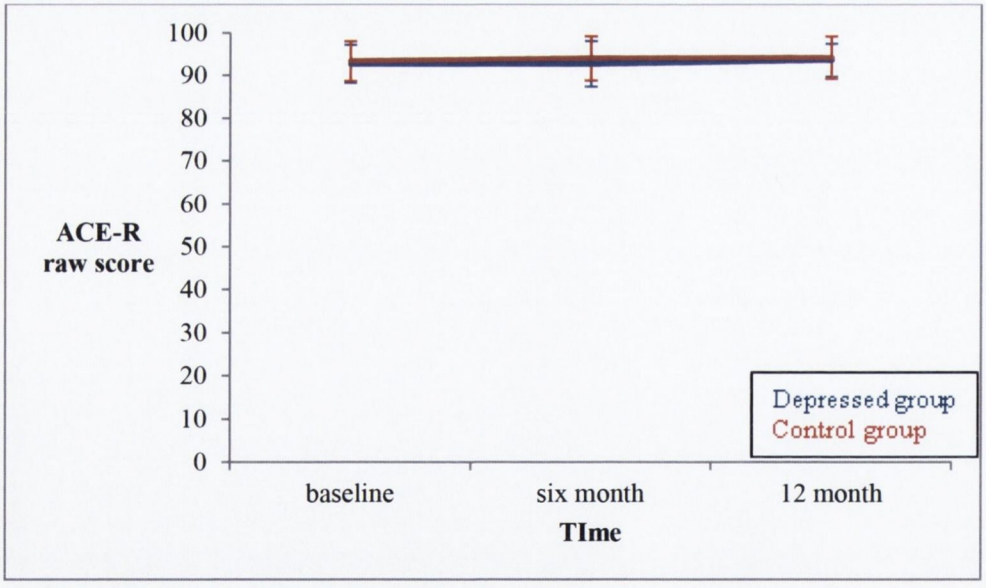


Figure 32 Addenbrooke's Cognitive Examination-Revised means (SD) over one year follow-up

Measure	Time	Depressed group n=11	Control group n=21	Comparison	F (df)	p value	Effect-Size
MMSE	Baseline	29.36 (0.8)	29.43 (0.7)	Group	0.355 (1)	0.556	0.012
	Six month	29.18 (0.9)	29.43 (0.7)	Time	0.154 (2)	0.858	0.011
	12 month	29.27 (0.9)	29.38 (1.1)	Group*Time	0.154 (2)	0.858	0.011

Table 40 Mini Mental State Examination means (SD) over one year follow-up

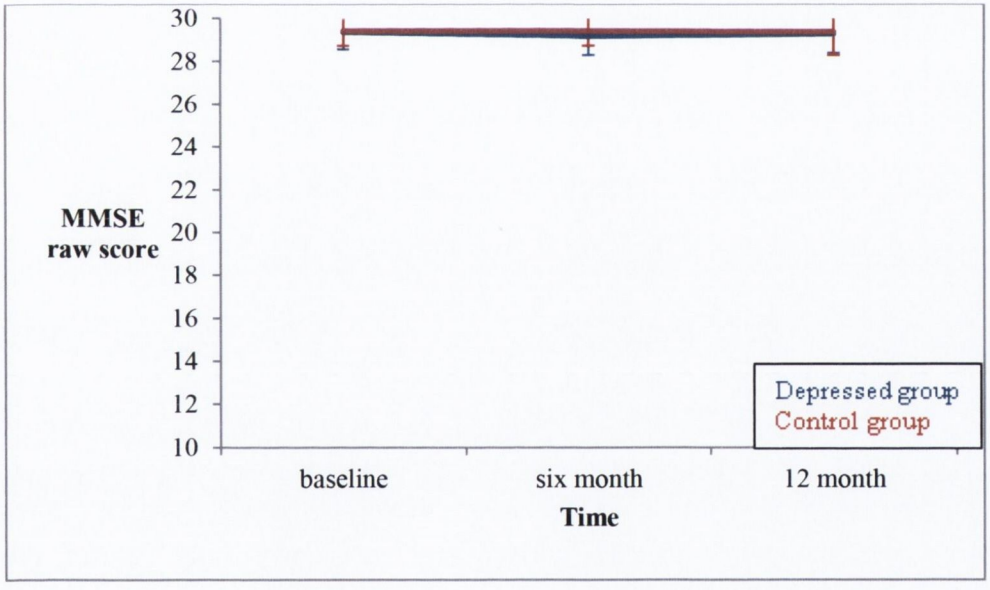


Figure 33 Mini Mental State Examination means (SD) over one year follow-up

5.3.2.3.2 Retrospective memory

Baseline AMI-SF raw scores of the participants in the follow-up depressed and control groups are presented in Figure 34. There was a significant difference between the depressed and control groups in this part of The Mem-Dep Study ($z=-3.992$, $p<0.001$). Original raw scores at baseline on the AMI-SF were converted to percentages, with the details provided by both groups representing 100% at baseline. Consistency of follow-up recall with baseline was then assessed at six and 12 month follow-up. Using the percentage consistency scoring method no significant interaction between group and time was found on the AMI-SF (Table 41, Figure 35). No significant differences were found for performance on the AMI-SF between groups, although the difference between groups over-time approached significance at $p<0.022$. It should be noted that the significant difference found between raw scores at baseline is not apparent here because all baseline scores were converted to 100%. Within groups over time there was a significant change in performance on the AMI-SF. Post-hoc tests indicated that scores were significantly different between baseline and six months and baseline and 12 months, with no difference between six months and 12 months. Further analyses with separate repeated measures ANOVA's showed this was true for both depressed participants ($p<0.001$) and controls ($p<0.001$).

No significant interaction was found between group and time on the Public Events Questionnaire. No significant differences were found for performance on the Public Events Questionnaire between groups. Within groups there was a significant change in performance on the Public Events Questionnaire, where scores increased in both groups over time (Table 42, Figure 36). Post-hoc tests indicated that scores were significantly increased from baseline to six months and from baseline to 12 months, but there was no difference between six months and 12 months. Further analyses with

separate repeated measures ANOVA's showed this was true for both depressed participants ($p=0.001$) and controls ($p<0.001$).

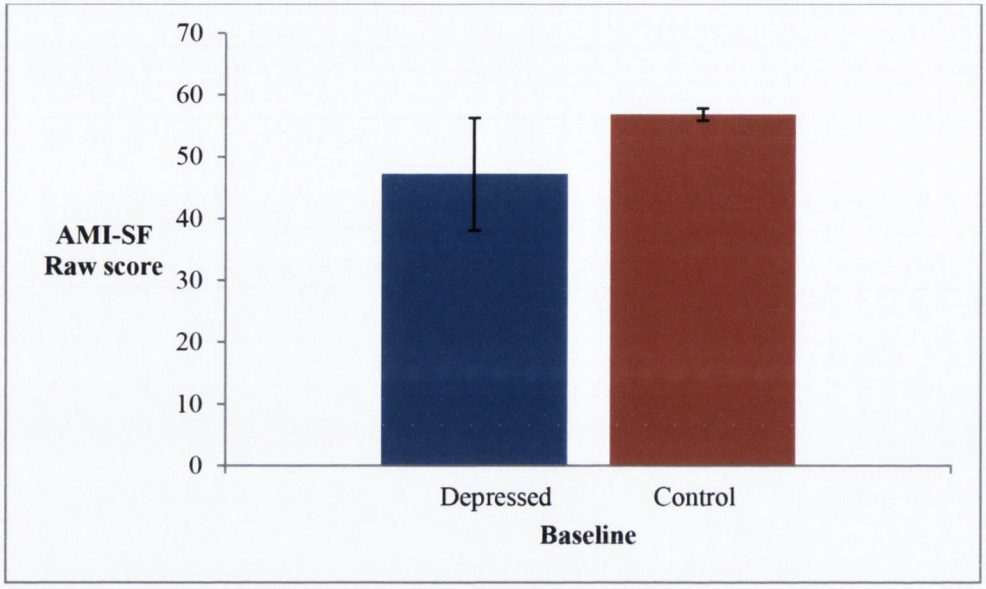


Figure 34 Baseline Autobiographical Memory Interview Short-form raw scores of the follow-up depressed and control groups

Measure	Time	Depressed group n=15	Control group n=21	Comparison	F (df)	p value	Effect-Size
AMI-SF	Baseline	100 (0.0)	100 (0.0)	Group	5.803 (1)	0.022	0.146
(% retained	Six month	71.40 (11.3)	79.38 (9.9)	Time	92.938 (2)	<0.001	0.857
from baseline)	12 month	66.93 (19.36)	77.42 (10.36)	Group*time	2.877 (2)	0.071	0.148

Table 41Autobiographical Memory Inventory-Short Form means (SD) over one year follow-up

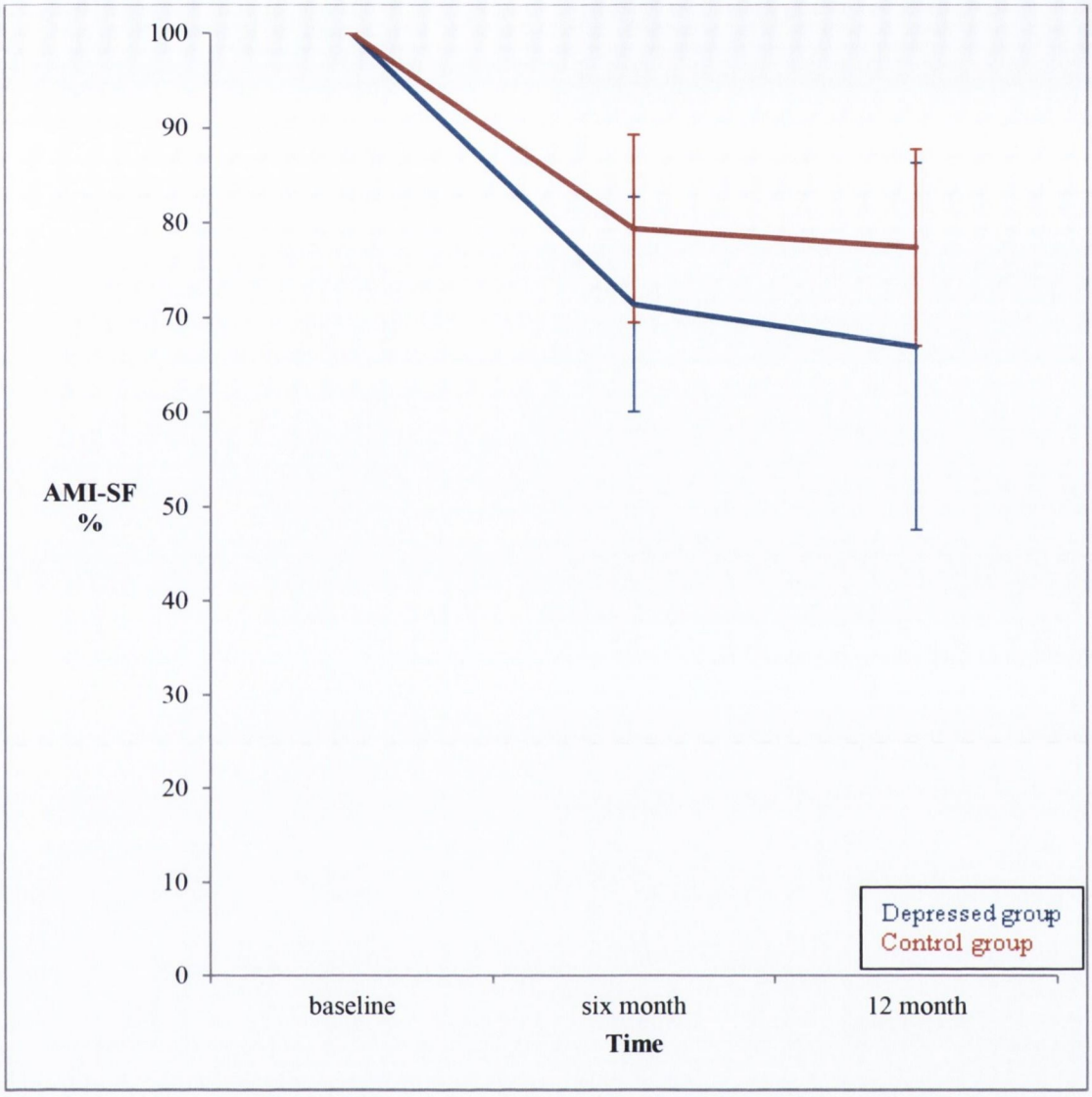


Figure 35 Autobiographical Memory Inventory-Short Form means (SD) over one year follow-up

Measure	Time	Depressed group n=15	Control group n=19	Comparison	F (df)	p value	Effect-Size
Public Events Questionnaire	Baseline	74.93 (18.0)	77.89 (18.0)	Group	0.104 (1)	0.750	0.003
	Six month	81.87 (17.6)	82.89 (19.0)	Time	34.105 (2)	<0.001	0.688
	12 month	83.07 (15.29)	84.89 (17.7)	Group*Time	0.666 (2)	0.521	0.041

Table 42 Public Events Questionnaire means (SD) over one year follow-up

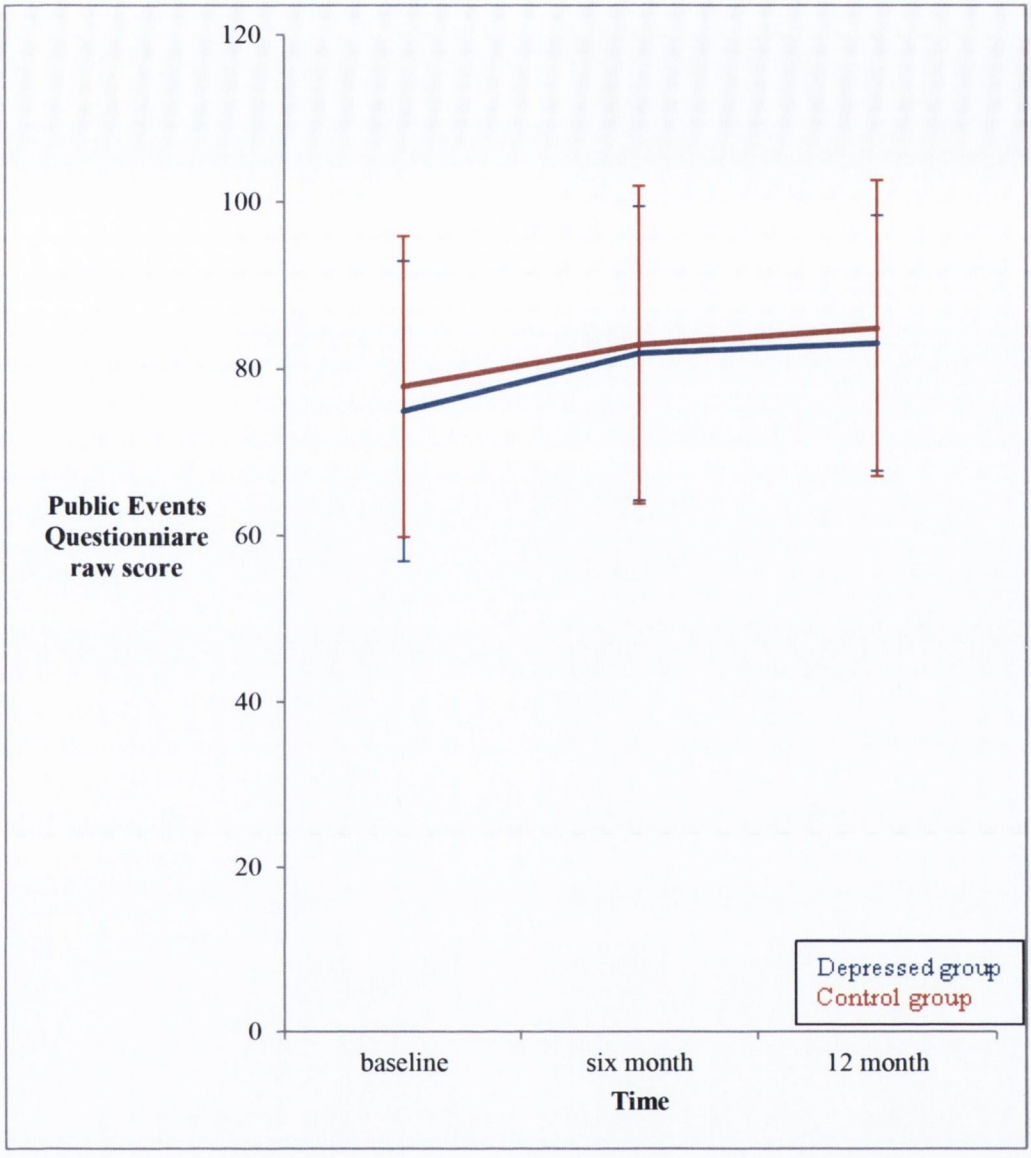


Figure 36 Public Events Questionnaire means (SD) over one year follow-up

5.3.2.3.4 Anterograde verbal learning and memory

No significant interaction was found between group and time on the Buschke FCSR, total immediate recall (learning), over six and 12 month follow-up. No significant difference was found between groups or within groups over time (Table 43, Figure 37).

No interaction was found between group and time on the Buschke FCSR free delayed recall task. No significant differences were found between groups or within groups over time (Table 44, Figure 38).

Measure	Time	Depressed group n=11	Control group n=21	Comparison	F (df)	p value	Effect-Size
Buschke FCSR	Baseline	33.09 (6.9)	33.67 (6.2)	Group	0.012 (1)	0.913	0.000
Immediate	Six month	35.27 (6.4)	34.38 (6.1)	Time	4.215 (2)	0.025	0.225
Recall (learning)	12 month	36.18 (7.3)	35.76 (7.3)	Group*Time	0.214 (2)	0.809	0.015

Table 43Buschke immediate recall means (SD) over one year follow-up

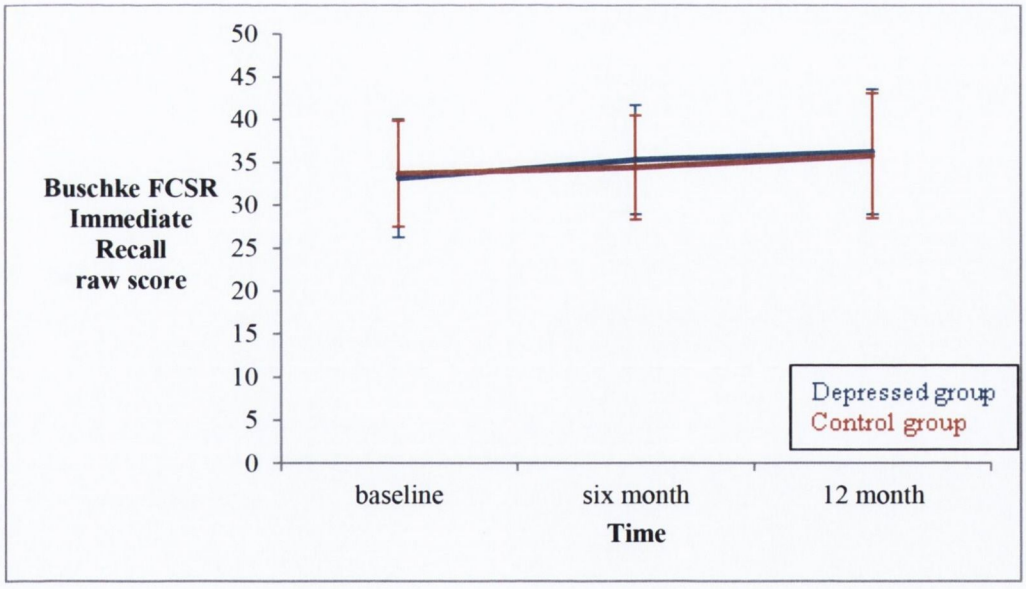


Figure 37 Buschke immediate recall means (SD) over one year follow-up

Measure	Time	Depressed group n=11	Control group n=21	Comparison	F (df)	p value	Effect-Size
Buschke FCSR	Baseline	13.36 (1.4)	13.05 (2.2)	Group	0.009 (1)	0.925	0.000
Free delayed	Six month	12.64 (2.1)	12.62 (2.3)	Time	1.388 (2)	0.266	0.087
Recall	12 month	13.00 (2.3)	13.52 (2.1)	Group*Time	0.788 (2)	0.464	0.052

Table 44Buschke delayed free recall means (SD) over one year follow-up

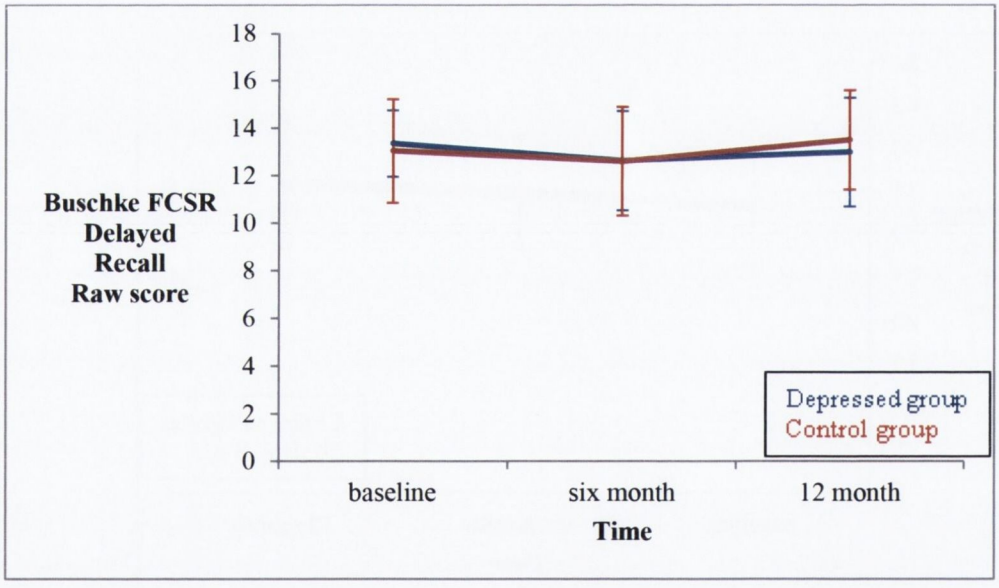


Figure 38 Buschke delayed free recall means (SD) over one year follow-up

5.3.2.3.5 Anterograde visual learning and memory

No significant interaction was found between group and time on the ROCF immediate recall task. Similarly, no significant differences were found for performance between groups. Within groups over time there was a significant increase in scores (Table 45, Figure 39). Post-hoc tests indicated that scores were significantly increased between baseline and six months and baseline and 12 months, with no difference between six months and 12 months. Further analyses with separate repeated measures ANOVA's showed this was true for both depressed participants ($p=0.004$) and controls ($p<0.001$).

No significant interaction was found between group and time on the ROCF delayed free recall task. Likewise, no significant differences were found for performance between groups. Within groups over time there was a significant change in performance on the delayed free recall task (Table 46, Figure 40). Post-hoc tests indicated that scores were increased significantly between baseline and six months and baseline and 12 months, with no difference between six months and 12 months. Further analyses with separate repeated measures ANOVA's showed this was true for both depressed participants ($p<0.001$) and controls ($p<0.001$).

Measure	Time	Depressed group n=11	Control group n=21	Comparison	F (df)	p value	Effect-Size
ROCF	Baseline	17.05 (8.3)	18.14 (6.7)	Group	0.671 (1)	0.419	0.022
immediate	Six month	22.14 (8.9)	24.62 (5.6)	Time	27.162 (2)	<0.001	0.652
recall	12 month	22.86 (6.7)	25.05 (6.7)	Group*Time	0.287 (2)	0.753	0.019

Table 45 ROCF immediate recall means (SD) over one year follow-up

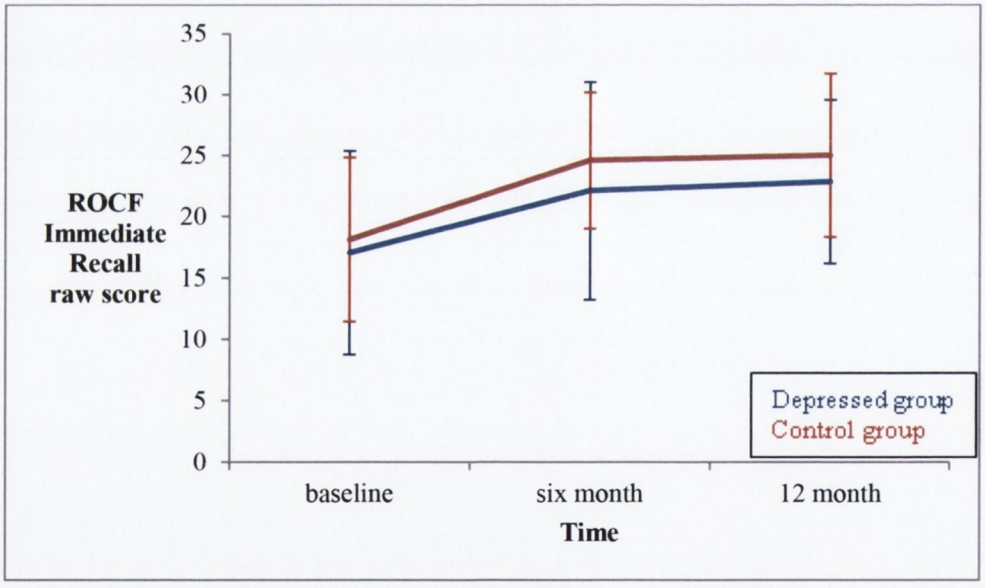


Figure 39 ROCF immediate recall means (SD) over one year follow-up

Measure	Time	Depressed group n=11	Control group n=21	Comparison	F (df)	P value	Effect-size
ROCF	Baseline	17.30 (6.6)	17.50 (6.5)	Group	0.003 (1)	0.958	0.000
delayed	Six month	25.10 (5.6)	23.76 (5.6)	Time	36.104 (2)	<0.001	0.721
recall	12 month	23.85 (7.5)	25.33 (6.1)	Group*Time	2.243 (2)	0.125	0.138

Table 46 ROCF delayed recall means (SD) over one year follow-up

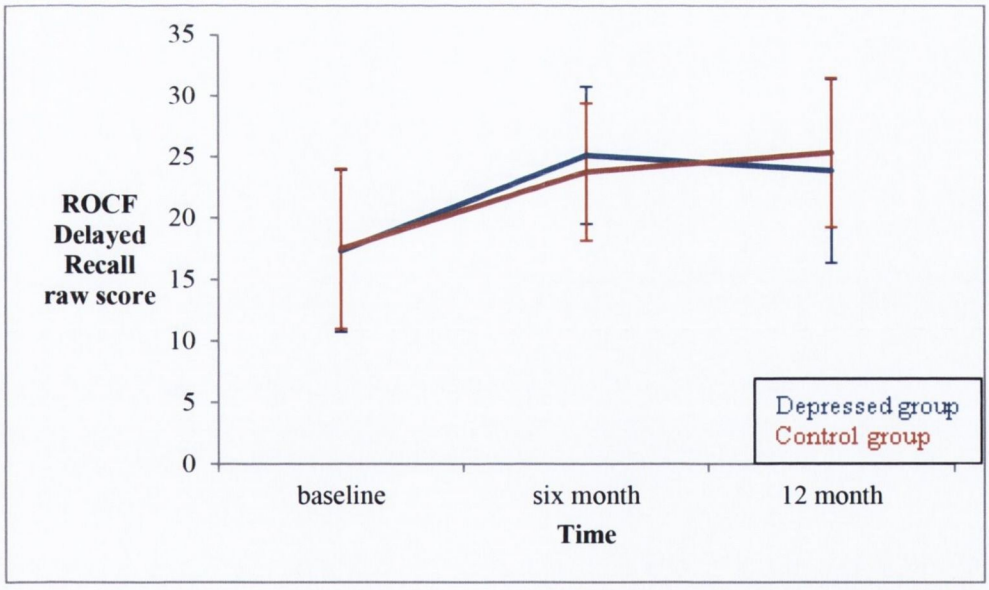


Figure 40 ROCF delayed recall means (SD) over one year follow-u

5.3.2.3.6 Attention and working memory

There was no significant interaction between group and time on the Digit Span Forwards. No significant differences were found for performance, over six and 12 month follow-up between groups or within groups over time (Table 47, Figure 41).

No significant interaction was found between group and time for performance on the Digit Span Backwards. No significant differences were found, on Digit Span Backwards between groups. Within groups a significant increase in scores was shown (Table 48, Figure 42). Post-hoc tests indicated that the significant differences were between baseline and six months, but not between baseline and 12 months or six months and 12 months. Repeated measures ANOVA's showed that differences were significant for controls (0.001) while scores of depressed participants approached significance (0.016).

Measure	Time	Depressed group n=9	Control group n=21	Comparison	F (df)	p value	Effect-size
Digit Span	Baseline	8.89 (2.9)	9.57 (2.0)	Group	3.232 (1)	0.083	0.103
Forward	Six month	8.56 (1.9)	10.19 (2.7)	Time	0.161 (2)	0.852	0.012
	12 month	8.11 (2.8)	10.19 (2.0)	Group*Time	1.425 (2)	0.258	0.095

Table 47 Digit Span Forward means (SD) over one year follow-up

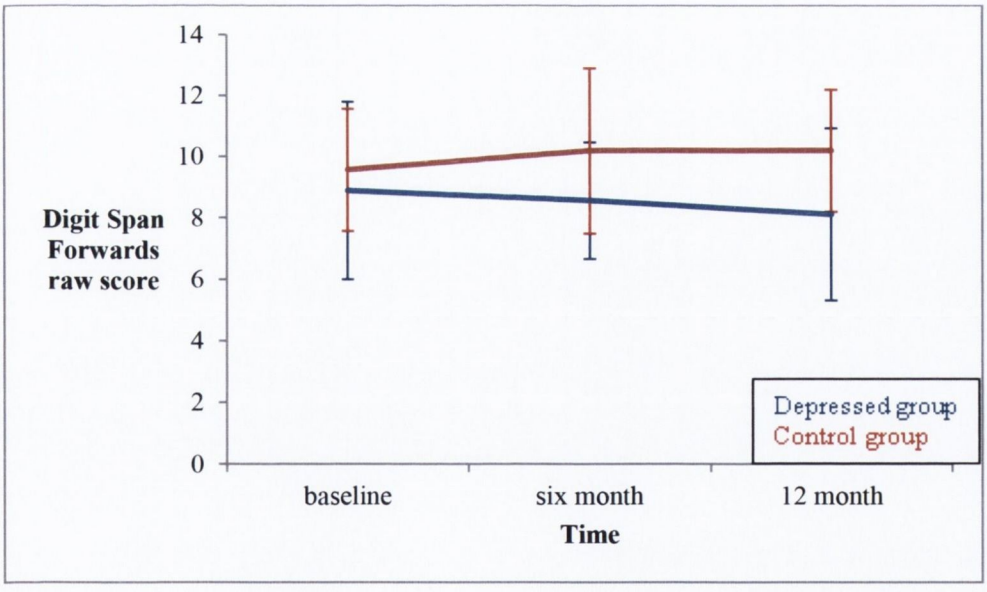


Figure 41 Digit Span Forward means (SD) over one year follow-up

Measure	Time	Depressed group n=9	Control group n=21	Comparison	F (df)	p value	Effect-size
Digit Span Backwards	Baseline	6.33 (2.5)	7.33 (1.7)	Group	2.362 (1)	0.136	0.078
	Six month	8.00 (2.7)	8.86 (2.3)	Time	13.373 (2)	<0.001	0.498
	12 month	7.00 (2.0)	8.38 (2.0)	Group*Time	0.164 (2)	0.849	0.012

Table 48 Digit Span Backwards means (SD) over one year follow-up

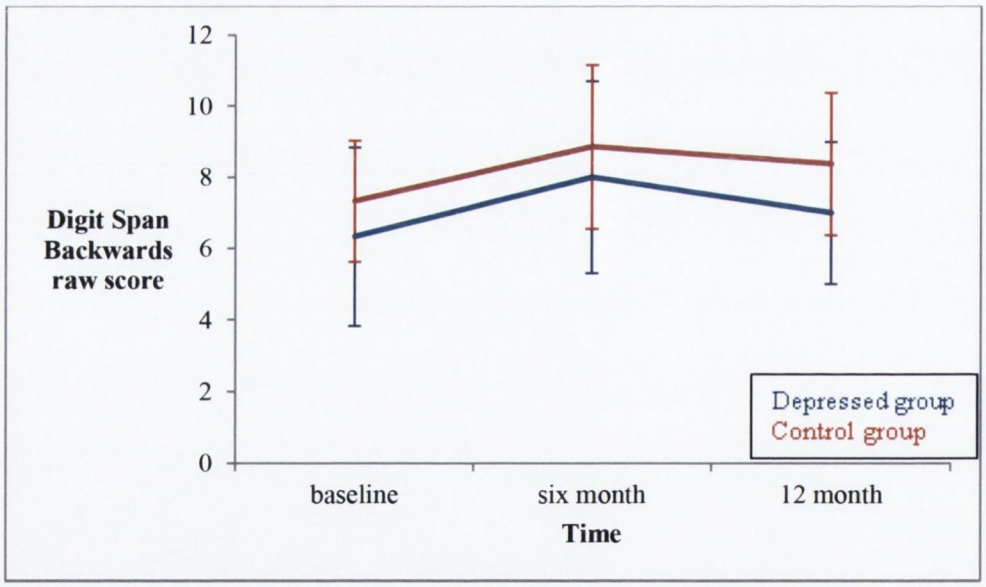


Figure 42 Digit Span Backwards means (SD) over one year follow-up

5.3.2.3.7 Psychomotor speed and processing

No significant interaction was found between group and time on the Grooved Pegboard Test, over six and 12 month follow-up. No significant differences were found for performance between groups or within groups over time (Table 49, Figure 43).

There was no significant interaction between group and time for performance on the Trail Making Test-A. Similarly, no differences were found over six and 12 month follow-up between groups or over time (Table 50, Figure 44).

Measure	Time	Depressed group n=11	Control group n=19	Comparison	F (df)	p value	Effect-Size
Grooved Pegboard Test (seconds)	Baseline	80.45 (18.5)	71.58 (13.0)	Group	2.754 (1)	0.108	0.090
	Six month	76.09 (15.2)	70.84 (13.8)	Time	0.940 (2)	0.403	0.065
	12 month	80.55 (17.7)	71.95 (12.6)	Group*Time	0.370 (2)	0.694	0.027

Table 49 Means (SD) of seconds taken to complete the Grooved Pegboard Test over one year follow-up

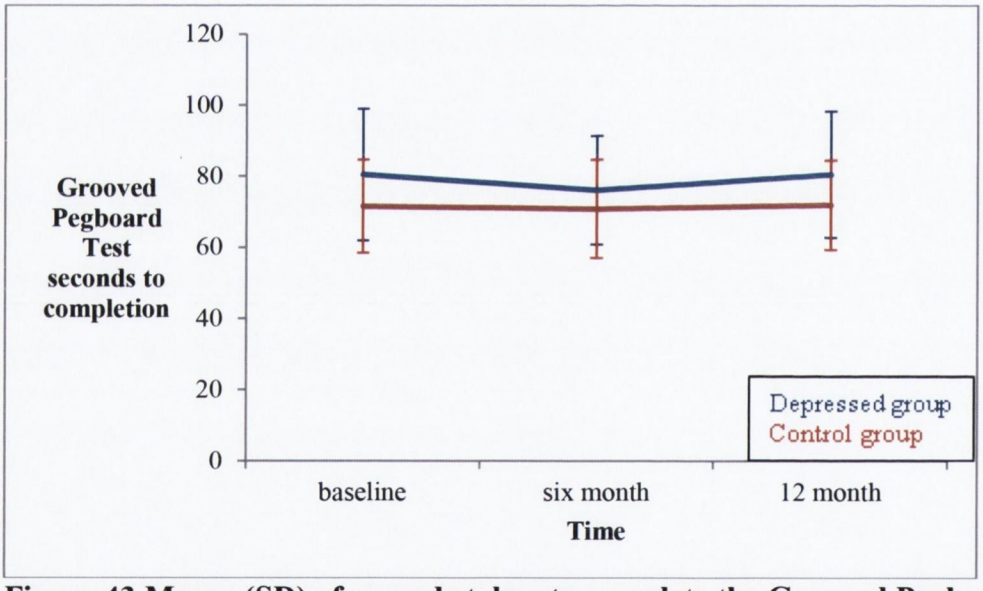


Figure 43 Means (SD) of seconds taken to complete the Grooved Pegboard Test over one year follow-up

Measure	Time	Depressed group n=11	Control group n=21	Comparison	F(df)	p value	Effect-size
Trail Making	Baseline	34.91 (10.7)	33.05 (11.8)	Group	0.897 (1)	0.351	0.029
Test A	Six month	32.45 (14.6)	28.14 (9.3)	Time	2.923 (2)	0.070	0.168
(seconds)	12 month	31.73 (12.1)	27.57 (10.2)	Group*Time	0.250 (2)	0.781	0.017

Table 50 Trail Making Test-A means (SD- in seconds) over one year follow-up

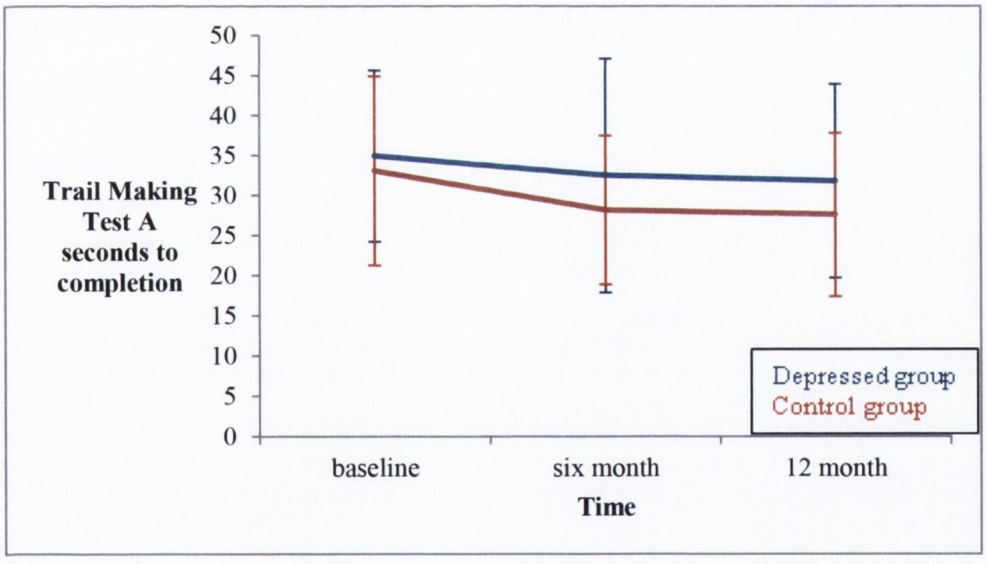


Figure 44 Trail Making Test-A means (SD- in seconds) over one year follow-up

5.3.2.3.8 Executive function

No significant interaction between group and time was found for performance on the TMT-B, over six and 12 month follow-up. No significant difference was found between groups or within groups over time (Table 51, Figure 45).

With regard to Category (semantic) fluency no significant interaction was shown between group and time. No significant differences were found for performance over six and 12 month follow-up between groups or within groups over time (Table 52, Figure 46).

No significant interaction was found between group and time for performance on the Letter (phonemic) fluency, over six and 12 month follow-up. There was no significant difference found between groups or within groups over time (Table 53, Figure 47).

Measure	Time	Depressed group n=11	Control group n=21	Comparison	F (df)	p value	Effect-size
Trail Making	Baseline	63.36 (19.2)	58.38 (22.5)	Group	0.937 (1)	0.341	0.030
Test B	Six month	62.45 (23.4)	58.52 (32.9)	Time	0.329 (2)	0.722	0.022
(seconds)	12 month	71.91 (35.5)	54.61 (23.4)	Group*Time	2.068 (2)	0.145	0.125

Table 51 Trail Making Test Part B means (SD, in seconds) over one year follow-up

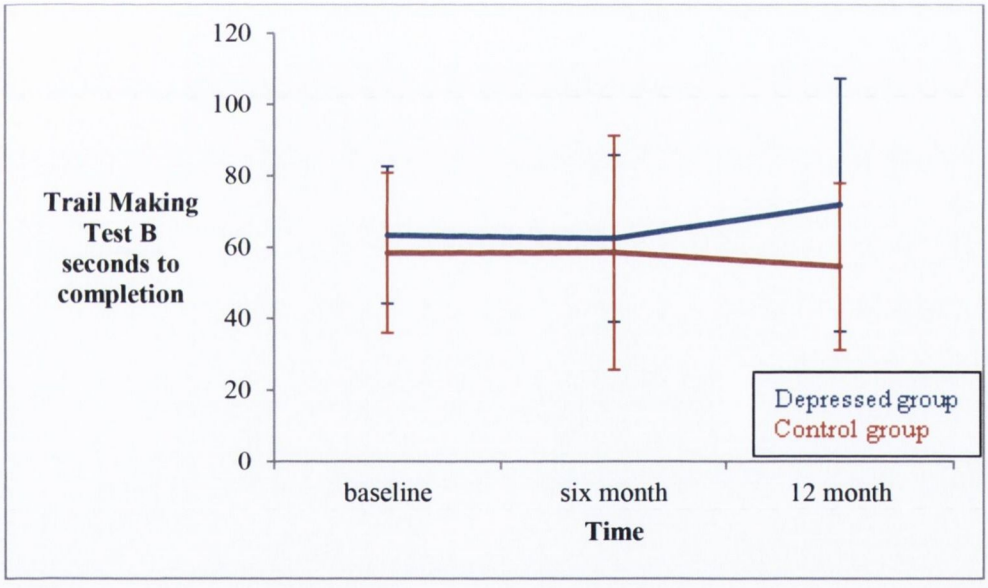


Figure 45 Trail Making Test Part B means (SD, in seconds) over one year follow-up

Measure	Time	Depressed group n=11	Control group n=21	Comparison	F (df)	p value	Effect-Size
Category Fluency	Baseline	20.73 (4.1)	22.24 (4.1)	Group	0.004 (1)	0.951	0.000
	Six month	20.73 (6.4)	20.24 (3.5)	Time	1.981 (2)	0.156	0.120
	12 month	22.09 (8.4)	20.76 (4.1)	Group*Time	1.474 (2)	0.246	0.092

Table 52 Category fluency means (SD) over one year follow-up

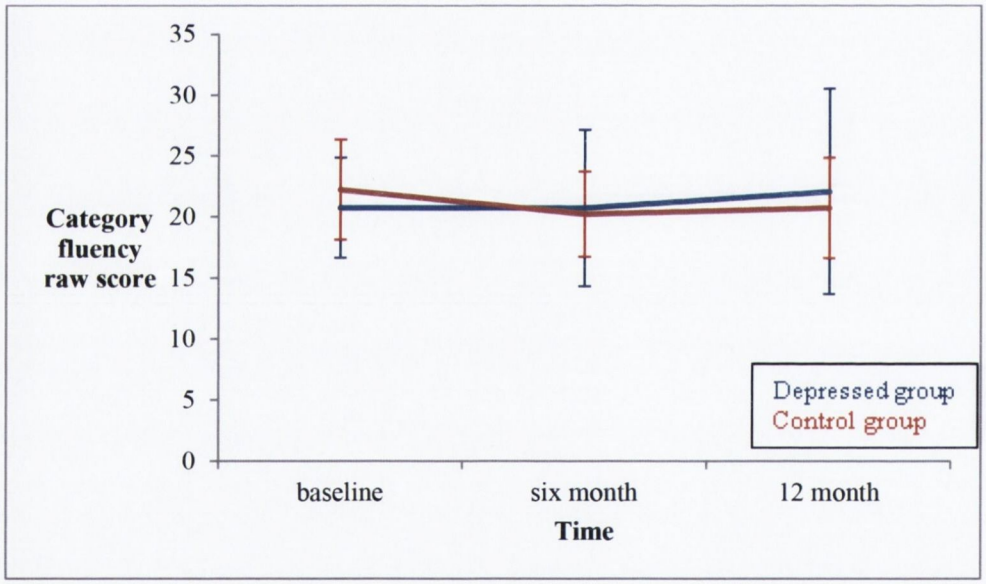


Figure 46 Category fluency means (SD) over one year follow-up

Measure	Time	Depressed group n=11	Control group n=21	Comparison	F (df)	p value	Effect-size
Letter Fluency	Baseline	16.00 (5.1)	14.48 (4.2)	Group	0.231 (1)	0.635	0.008
	Six month	14.64 (5.9)	15.24 (4.6)	Time	0.217 (2)	0.806	0.015
	12 month	16.00 (5.9)	14.67 (3.8)	Group*Time	0.221 (2)	0.221	0.099

Table 53 Letter fluency means (SD) over one year follow-up

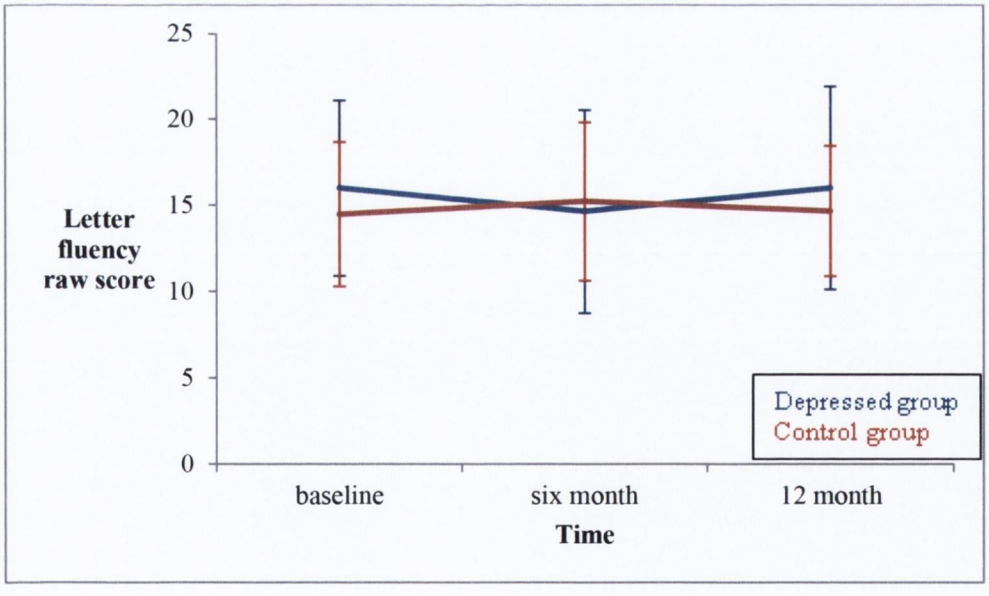


Figure 47 Letter fluency means (SD) over one year follow-up

5.3.2.4 Effect of depression severity on cognitive function over one year follow-up

Due to the low numbers of depressed participants who completed follow-up assessments at both six and 12 months, it would not have been representative to divide the group further into remitters/responders and non-remitters/responders to treatment, in order to examine the effect of persisting depressive symptomology on cognitive function. Instead, the relationship between depression severity and cognitive function has been assessed by correlating HDRS-24 scores with measures of cognitive function at each time-point. Both depressed and control participants were included in this analysis to examine the effect of a wide range of scores on the HDRS-24 on cognitive function. This allowed for interpretation of any relationships found with reference to a non-depressed population.

The HDRS-24 was not normally distributed at any time-point and as such correlations were conducted using Spearman's rho as a non-parametric alternative to Pearson's product-moment correlation. All correlations are presented in Table 54 and discussed below.

Measure		baseline		6 month		12 month	
	n	p value	rho	p value	rho	p value	rho
BPRS	36	<0.001	0.876	<0.001	0.949	<0.001	0.877
BDI-II	35	<0.001	0.890	<0.001	0.746	<0.001	0.651
ACE-R	36	0.464	-0.126	0.058	-0.334	0.396	-0.155
MMSE	36	0.609	-0.088	0.621	-0.089	0.786	-0.050
AMI-SF	36	<0.001	-0.602	0.077	-0.289	0.027	-0.368
Public Events	36	0.311	-0.174	0.800	-0.045	0.150	-0.252
Buschke FCSR immediate recall	34	0.654	-0.080	0.782	-0.051	0.626	0.090
Buschke FCSR delayed recall	34	0.653	0.080	0.735	-0.062	0.714	-0.067
ROCF immediate recall	34	0.661	0.078	0.073	-0.321	0.410	-0.151
ROCF delayed recall	33	0.462	0.133	0.190	-0.238	0.729	-0.064
Digit Span Forward	34	0.473	-0.127	0.452	-0.143	0.022	-0.404
Digit Span Backward	34	0.063	-0.323	0.034	-0.389	0.318	-0.182
Grooved Pegboard	33	0.195	0.231	0.203	0.231	0.453	0.140
TMT-A	34	0.601	0.093	0.009	0.454	0.949	-0.012
TMT-B	34	0.279	0.191	0.002	0.531	0.504	0.123
Category fluency	36	0.252	-0.196	0.980	0.004	0.500	-0.122
Letter fluency	36	0.641	0.080	0.551	-0.104	0.231	-0.214

Table 54 Correlations of clinical and cognitive measures with the Hamilton Depression Rating Scale (24-item)

At all time-points the HDRS-24 was significantly correlated with scores on the BDI-II and the BPRS ($p<0.001$) as would be expected.

At baseline the only cognitive measure to correlate significantly with the HDRS-24 was the AMI-SF, where more severe depression was related to a lower performance on the AMI-SF ($p<0.001$, rho= -0.602).

At six month follow-up significant relationships with the HDRS-24 were found for both the TMT-A ($p=0.009$, rho=0.454) and the TMT-B ($p=0.002$, rho=0.531) where more severe depression was associated with longer length of time to complete the tasks. Other moderate, though non-significant, correlations were found at six months between the HDRS-24 and the Digit Span Backwards ($p=0.034$, rho= -0.389) and the ACE-R ($p=0.058$, rho= -0.334), indicating that higher scores on the HDRS-24 were associated with worse performance on each task.

No significant correlations were found between HDRS-24 scores and performance on cognitive measure at 12 month follow-up. Moderate non-significant correlations were noted between the HDRS-24 and the AMI-SF ($p=0.027$, rho= -0.368) and the Digit Span Forwards ($p=0.022$, rho= -0.404), again indicating that more severe depression was correlated with worse performance on these two cognitive variables.

5.3.2.5 Summary of cognitive findings

Performance on cognitive measures did not differ between groups at the $p\leq0.01$ level, over the 12 month follow-up. Difference in performance between groups on the AMI-SF was significant at baseline when raw scores were compared, but only approached significance at $p=0.022$ when consistency with baseline at follow-up was assessed. Again, depressed participants were less consistent in recall of autobiographical memory than controls at six and twelve months.

Over time both measures of retrospective memory changed significantly within groups. Performance on the AMI-SF dropped significantly between baseline and six month and baseline and 12 month follow-up, for both depressed and control participants. Performance on the Public Events Questionnaire increased significantly for both groups between baseline and six month and baseline and 12 month follow-up. Neither the AMI-SF nor the Public Events Questionnaire showed significant change in performance for either group between six and 12 month follow-up.

Performance on visual learning and memory, for both the ROCF immediate recall and delayed recall tasks, increased significantly for depressed and control participants between baseline and six month and baseline and 12 month follow-up. There was no further increase in performance between six and 12 month assessment for either group.

There was a significant improvement in performance on the Digit Span Backwards for control participants between baseline and six month follow-up. Improvements in performance in the depressed group on the Digit Span Backwards approached significance ($p=0.016$) between baseline and six month follow-up.

Correlations were performed to assess the relationship between depression severity and cognition over each time-point. At baseline better performance on the AMI-SF was significantly related to less severe depression as measured by the HDRS-24. At six months more severe depression was linked to taking longer to complete the TMT-A and TMT-B, measures of psychomotor speed and processing and executive function respectively. More severe depression was also related to lower scores on the ACE-R and the Digit Span Backwards task, although these moderate correlations were not significant. Similarly, no significant correlation was found for the AMI-SF and the Digit Span forwards despite moderate negative correlations being shown.

5.4 Discussion

A sub-group of the depressed and control participants from the baseline study (see section 4.3.1) who completed follow-up assessments at both six and 12 months took part in this longitudinal arm of The Mem-Dep study. Participants completed the same clinical and cognitive assessments in both groups at all time-points (with alternative versions where available).

Overall, the groups differed significantly on clinical measures of depression at all time-points, with the exception of the BDI-II at 12 months, though depressed participants still scored higher on this measure than controls. With regard to cognitive differences between groups, no statistically significant differences were found between the depressed and control groups for any cognitive measures over 12 months follow-up, although performance on the AMI-SF approached significance, with the depressed group scoring lower at all time-points. Significant changes over time within both the depressed and control groups were found on the AMI-SF, Public Events Questionnaire, ROCF immediate recall and ROCF delayed recall, with significant change between baseline and six month and baseline and 12 month follow-up, but no change between six and 12 month follow-up for each measure. A significant change was found in controls between baseline and six months on the Digit Span backwards, while performance for the same time-period approached significance for depressed participants. At baseline the AMI-SF was significantly correlated with depression severity. At six months poorer performance on the TMT-A and TMT-B were associated with more severe depressive symptoms, and at 12 months there were no significant correlations between cognition and depression severity, although performance on the AMI-SF and Digit Span Forward approached significance. These results will now each be discussed in more detail.

5.4.1 Clinical measures

Findings on clinical measures for the control group over time were in line with what would have been expected, in that controls scored in the very low range on all clinical mood and symptom assessments and this did not change significantly over time. Similarly, the fact that the depressed group scored significantly higher than controls on all clinical measures at baseline was expected, especially because the groups had been chosen according to criteria of currently having or never having a depressive episode. However, scores in the depressed group on all clinical measures (HDRS-24, BDI-II and BPRS) remained significantly higher than controls at six months follow-up and again for the HDRS-24 and BPRS at 12 month follow-up. This was somewhat unusual as it might be expected that two thirds of this group would have remitted after treatment (Rush et al., 2006). In this particular group just under half the depressed group (6 of 15) met remission criteria at 12 months (i.e. HDRS-24 $\leq$8 and $\geq$60% decrease in score from baseline). It must also be noted that there was no further significant drop in HDRS-24 scores in the depressed group from six month to 12 month follow-up, and mean scores only dropped by a couple of points in this time. This indicates that participants only improved to a certain level and then largely stayed at that level beyond six months. It is unclear whether this represents a limit to the improvement in depression severity for the depressed group or whether this would reduce further over time. As a result the depressed group as a whole remained significantly more depressed than controls on the HDRS-24 at 12 month follow-up. A recent study that examined outcome of unipolar depression patients, treated at specialist depression centres in Australia, found that at 12 week follow-up only 8.8% of participants achieved full remission with no relapse, whereas a further 3.1% achieved remission but relapsed within two months (Hansen et al., 2012). The authors of the Australian study speculated that this low remission rate

might have been linked to the fact that people referred to specialist centres for treatment of depression are often suffering from severe or treatment resistant depression. As the Mem-Dep study was also carried out in a specialist psychiatric hospital it is possible that the participants in this study were also suffering from severe depression, which may be reflected in the remission rates.

5.4.2 Cognitive measures

No differences were found between groups or within groups over time for performances on the ACE-R and MMSE, both used as measures of global cognition. Both controls and depressed participants scored in the normal range on the ACE-R and MMSE at all times (Mioshi et al., 2006), thus indicating no severe cognitive impairment to begin with in either group. Results from the rest of the cognitive testing will be discussed for retrospective memory firstly, followed by a separate discussion of anterograde verbal and visual memory, attention, psychomotor speed and processing and executive function.

5.4.2.1 Retrospective memory

Original raw scores at baseline on the AMI-SF were converted to percentages, with the details provided by both groups at baseline representing 100 percent. Consistency of follow-up recall with baseline was then assessed at six and 12 month follow-up. Consistency on the AMI-SF was lower at six and 12 month follow-up for depressed participants compared to controls and this effect approached significance. This finding suggests that depressed participants have more difficulty in recalling previously remembered details than healthy controls and this effect persists despite an improvement in depressive symptoms. In addition, correlational analyses showed that

performance on the AMI-SF was significantly related to depression severity at baseline and this relationship approached significance at 12 month follow-up. These results, though just outside the criteria for statistical significance, provide support for the conclusion that autobiographical memory is impaired during a depressive episode, and also, importantly, that autobiographical memory is affected by depression severity. These results are in line with results from other research that has found that depressed participants are less able to produce autobiographical memories that healthy controls (Sumner et al., 2010, van Vreeswijk and de Wilde, 2004, Williams et al., 2007, Gallassi et al., 2006) and builds on those findings by demonstrating that this continues to affect depressed participants up to 12 months later, despite the fact that depression scores have decreased. This finding is similar to a previous study that showed that remitted depressed participants remained impaired at six months compared to controls at baseline, despite a significant increase in scoring on an autobiographical memory measure within the depressed group from baseline to six month follow-up (Gallassi et al., 2006). However, as noted above, the depressed participants in The Mem-Dep Study did not completely remit and remained significantly more depressed than controls at 12 months. As such, the persisting deficit in autobiographical memory function compared to controls may be due to persisting low mood. Nevertheless, these results are, to the best of my knowledge, the first to examine the consistency of autobiographical memory at 12 month follow-up in a depressed group, and the first to examine both depressed participants (not receiving ECT) and healthy controls up to one year after initial assessment with the AMI-SF or any other autobiographical memory questionnaire.

The second notable finding regarding autobiographical memory comes from the assessment of controls over time. Results showed that both depressed and control participants had a significant decrease in consistency of autobiographical memory

between baseline and six month follow-up. This finding is important because it allows for interpreting the loss of memory in depression in terms of what happens normally over time. Thus, when the average scores over each assessment point are analysed, it is apparent that, in total, the depressed group were not consistent in recalling just over ten percent more memories than controls failed to recall. This is notably different to how this finding could be interpreted without comparing it to controls, which would be that the depressed group could not consistently recall 33 percent of memories from baseline, in the absence of reporting that the control group also could not consistently recall 22 percent of baseline memories.

This finding has implications for previous research that has used the AMI-SF, for example in ECT studies that do not have a control group at all follow-ups (Calev et al., 1991, Sackeim et al., 1993, Sackeim et al., 2000, Sackeim et al., 2007). As seen above, to not have a comparison group at all times would have greatly inflated the perceived impairment in the clinical groups at follow-up. Not only does this underline the importance of including a control group at all follow-up times, it also reinforces the fact that memories are naturally lost over time in healthy participants (Ebbinghaus, 1885) and normative data should always be taken into account. Overall, depressed participants produced less autobiographical memories at baseline, and lost memory at a greater rate than controls over time, however differences between groups did not reach statistical significance.

Performance on the second measure of retrospective memory, the Public Events Questionnaire, contrasted markedly with findings regarding autobiographical memory function. There was no difference at any time between depressed participants and controls on the Public Events Questionnaire. Again there was a significant change over time for both depressed and control participants on the Public Events Questionnaire, but

this time an increase in scores was seen in both groups between baseline and six month follow-up. This increase is due to the practice effect on the Public Events Questionnaire, as discussed in section 3.3.1.4. These findings are comparable to an earlier study that showed no differences between depressed and control participants at baseline, and a significant increase in controls performance between baseline and six month follow-up (Gallassi et al., 2006). It is also comparable to previous studies that showed a high level of consistency on repeat testing of depressed participants after seven months (Calev et al., 1989, Squire et al., 1981) and controls at one-month follow-up (Bizzozero et al., 2004) on public events memory measures.

The findings of the retrospective memory questionnaires put forward a number of interesting questions regarding the dissociable nature of retrospective memory and the effect of depression upon it; and the consistency of retrospective memories over time. The finding that public events memory is more consistent than autobiographical memory over time, for both depressed and control participants, adds strength to previous research that has shown that elements of retrospective memory may be dissociable, such as episodic and semantic memory (Piolino et al., 2002, Piolino et al., 2007) and autobiographical and public events memory (Gallassi et al., 2006). In this way these findings add to the theories of memory as a multi-component entity (Atkinson and Shiffrin, 1968, Baddeley and Hitch, 1974, Squire and Zola-Morgan, 1991, Tulving, 1983).

Building from this, the finding that autobiographical memory is likely to be more affected in the depressed group than the control group, both at baseline and over time, with the finding that public events memory is not worse in the depressed group than in controls, suggests that depression itself can affect these two facets of retrospective memory differently. Previous studies of autobiographical memory in

depression have tended to focus on the phenomenon of overgeneral memory ((Williams, 1988) whereby depressed groups are found to produce less detailed, more general personal memories than controls. Although the interest is in consistency of autobiographical memories in the current study, it was also found that depressed participants produced fewer memories than controls at baseline and that depressed participants were less consistent in providing details of previously recalled memories over time.

Researchers investigating overgeneral memory in depression have proposed that overgeneral recall may be a function of passive avoidance, whereby the depressed individual stops the memory search earlier than normal controls would in order to avoid unwanted or difficult recollections (Williams et al., 2007, Conway and Pleydell-Pearce, 2000). Clearly this theory suggests that it is the personal nature of the memories that causes disruptions at recall level. This may help to explain why autobiographical memory function is impaired in depression, while public events memory remains unaffected. However, the other notable finding in this study of retrospective memory is the fact that healthy controls do not consistently recall the same details when asked to recall the same autobiographical memory on a number of occasions. This cannot be attributed to the passive avoidance theory as discussed regarding depressed participants. This type of finding has also been noted in studies that examine the consistency of flashbulb memories over time, where it was shown that consistency of flashbulb and everyday (autobiographical) memories decrease by approximately 30 percent over one year (Talarico and Rubin, 2003) in healthy participants.

As noted above, it may simply be the case that a certain amount of memories are lost over time as Ebbinghaus described over one hundred years ago (Ebbinghaus, 1885). However, an interesting possibility involves the theory of memory re-consolidation and

how memory may be stored in an altered form each time it is recalled after initial encoding (Nadel and Hardt, 2011), that is, that the memory trace may be altered rather than strengthened each time it is retrieved. If this was the case then we should see an alteration in both autobiographical and public events memories, unless the effect is specific to memories of an episodic or autobiographical nature. To my knowledge, there have been no studies that have specifically investigated this effect to date, however it may be likely that the wealth of information that accompanies an autobiographical recollection (the autonoetic elements, whereby the event is re-lived rather than just remembered, (Irish et al., 2008, Wheeler et al., 1997)) leave the autobiographical memory more open to distortion that the public events memory.

5.4.2.2 General cognitive function over time

Overall, depressed participants performed lower than controls on measures of attention, psychomotor speed and processing, one executive function measure (Trail Making Test, part B) and immediate visual memory recall. However, the differences in performance between groups were not statistically significant for any cognitive measures. There were no differences in performance between the two groups on measures of verbal learning and memory, letter and category fluency and delayed visual memory recall. In addition, changes over time in the depressed group were mirrored in the control group. Each functional group of measures will be discussed in more detail.

Anterograde verbal learning and memory

Anterograde verbal learning and memory performance was not affected by depression at any time-point in this study. This finding contrasts with some previously reported studies where depressed participants were impaired at baseline and follow-up

compared to controls at baseline (Gallassi et al., 2006) and where performance was related to depression severity at follow-up (Gallagher et al., 2007). This difference may be due to the test used in The Mem-Dep Study, the Buschke FCSR. As discussed in section (2.1.3.5) the FCSR procedure aids encoding by having participants remember words from specific categories. This leads to enhanced encoding in an effort to ensure that results on the delayed recall task can be confidently attributed to memory performance, not encoding processes. As such, findings here suggest that when encoding is supported no memory impairments are apparent in the depressed group. This is supported by a previous meta-analysis that found that depression is associated with an impairment in effortful encoding of information (Zakzanis et al., 1998).

Anterograde visual learning and memory

In a similar manner, anterograde visual immediate and delayed memory recall were not significantly impaired in depressed participants compared to controls, although the depressed group averaged a worse performance on the immediate recall tasks than controls. The significant increase in scores of both groups between baseline and six month follow-up on both the ROCF immediate and delayed recall is likely to reflect the fact that both the Taylor complex figure and the Medical College of Georgia figures are slightly easier than the original Rey-Osterrieth complex figure (Fastenau et al., 1999) (see section 2.1.3.6). One previous longitudinal study that used the original Rey figure on both testing occasions found no significant change between baseline and follow-up in a depressed group (Biringer et al., 2007), while another found improved performance from baseline at six months follow-up on a visual reproduction task (Wechsler Memory Scale (Wechsler, 1981)) despite the fact that these participants were not impaired at baseline. With regard to the effect of depression severity on visual memory

performance, no correlation was found at any time between the immediate and delayed tasks on the ROCF and the HDRS-24. Again, this supports the idea that visual memory is not adversely affected in depression, and is in line with previous longitudinal findings that show no difference in change scores between remitters and non-remitters at approximately four months follow-up (Gallagher et al., 2007).

Attention and working memory

Findings of lower performance, but no significant difference from controls, for attention are in line with some previous studies that found no impairment of simple attention in depression (Gallassi et al., 2006, Veiel, 1997). Over time, depressed and control participants did not change significantly on Digit Span Forwards performance, although controls' span increased by approximately half a point at 12 months compared to baseline, whereas depressed participants performance dropped by the same amount. This may explain the moderate negative correlation at 12 months between Digit Span Forwards and depression severity.

Previous research has reported significant improvements from baseline in Digit Span Forward scores in depressed groups who have remitted (Biringer et al., 2007, Gallassi et al., 2006), even when participants were not impaired at baseline (Gallassi et al., 2006). Although the sample of depressed participants in the current study had significantly improved HDRS-24 scores at follow-up, only six participants remitted and one responded, and on average the group remained significantly different from control at six and 12 month follow-up, which may explain these contrasting findings. Similarly, performance of depressed participants on the Digit Span Backwards, assessing working memory, was lower, but not significantly different to controls at all times. Both groups displayed improved performance between baseline and six month

follow-up, followed by a return to baseline levels at 12 month assessment. The improvement at six month may have been due to the parallel version of the test use, rather than an actual improvement in performance, as both groups improved on the second assessment and return to baseline levels on the third. As working memory is often grouped with attention it is difficult to assess how common this finding is, although it is comparable to at least one other study (Gallassi et al., 2006) where no impairment was demonstrated in working memory at baseline and no change was found over time.

Psychomotor speed and processing

Performance on both measures of psychomotor speed and processing (TMT-A and Grooved Pegboard test) was again lower at all times for the depressed group, but not significantly lower than controls, suggesting that attention may be only mildly affected in unipolar depression. In addition, there were no significant changes over time for either group, although both depressed and control scores improved across time on the TMT-A between baseline and six month follow-up, which would appear to be a practice effect as controls improved more than depressed participants at this time-period. However, that makes it difficult to explain why there was a significant relationship between depression severity and performance on the TMT-A at six month follow-up. Previous research has reported no significant differences between responders and non-responders at six month follow-up, but that non-responders still score lower than responders (Douglas et al., 2011). Thus, following on from above, it seems that depression severity may affect psychomotor speed and processing, though this effect is likely to be small.

Executive function

Findings regarding executive function over time were mixed. Performances on measures of fluency (phonemic and semantic) were found not to be impaired compared to controls and there were no significant changes in either group over time, although depressed participants had improved category fluency scores at 12 months compared to baseline. However performance on the TMT-B, as a measure of cognitive flexibility, was lower in depressed participants than controls, though not significantly so, and decreased over time. There was no significant change in either group over time; however there was a significant negative correlation between depression severity and performance on the TMT-B at six month follow-up. These findings are similar to those found previously (Trichard et al., 1995) whereby verbal fluency improved with decrease in depression severity, while performance on the STROOP test remained impaired compared to controls at follow-up. They are also in line with a study in which non-symptomatic unipolar depressed patients performed significantly worse than healthy controls on the TMT-B (Paradiso et al., 1997), although in The Mem-Dep Study the difference between groups was not significant. Thus, these findings add support to the idea that some executive functions may be affected by depression severity, while others are less likely to be affected.

5.4.2.3 Conclusions

Overall, autobiographical and public events retrospective memory function were found to be differentially affected in depression and over time, with autobiographical memory being more affected by depression and less consistent over time, in both depressed and control groups, than public events memory. In addition, depression may lead to mild impairments in attention, psychomotor speed and processing, and some aspects of executive function, compared to controls, but the evidence for this in the

present study is not conclusive. Verbal memory deficits in depression may be linked to encoding deficits which are not apparent when strategies to promote initial encoding are employed.

5.4.2.4 Limitations, strengths and future directions

One limitation of the current study is the use of non-standardised assessments to assess autobiographical and public events memory. While this is generally unavoidable when using public events questionnaires due to the fact that they need to be updated and tailored to use with specific populations before use, every effort has been made to demonstrate that the Public Events Questionnaire in this study is reliable across versions and across time (Chapter 3). The AMI-SF, used to assess autobiographical memory, does not have normative data published to date. However the use of healthy controls at each assessment point in the current study allows the findings to be interpreted in light of the performance of a control group.

A second limitation of this study is the small number of depressed participants who completed each assessment at the six month and 12 month follow-up time-points, thus limiting the statistical power to detect differences between groups. Adding to this is the fact that a more stringent significance value was also employed to account for multiple testing. Low numbers are often a problem in real-world clinical research and reflect the difficulty in retaining severely and chronically depressed participants in a longitudinal study. The sample size in the study might have been larger had we included participants with bipolar depression. However, while some studies have found little difference between bipolar and unipolar patient groups in terms of the cognitive profile (Bearden et al., 2005), others have shown differences between the groups, with one

recent meta-analyses finding that those with bipolar depression perform worse than up on tests of IQ, rule discovery and word association (Stefanopoulou et al., 2009). The finding that unipolar depression may be associated with less cognitive impairment may provide some explanation for the limited amount of differences seen in the current work, between unipolar depressed participants and healthy controls.

Despite these limitations the study also has numerous strengths. To maintain the integrity of the depressed sample assessed and control for confounding variables, the criteria for entering the study were tight and did not accept any depressed participant with any history of previous ECT, bipolar depression or any other comorbid diagnoses, bar secondary anxiety. Thus, one of the strengths of the study is the fact that the depressed group is not confounded by mixed diagnoses or possible previous memory impairment due to ECT. A second strength of this study is the longitudinal design with the depressed sample being assessed up to one year after the initial assessment. Furthermore, the inclusion of a healthy control group at each assessment, allowing for a comparison of change in the depressed group to change over time in a normal population, is a very important strength of the current work. Finally, this study also addresses the issue of retrospective memory, using two separate tests of autobiographical memory and a specially constructed test of public events, and examined how they were affected both during an episode of depression and in recovery. This is a consideration that is often overlooked in studies of cognitive functioning in depression and, as has been shown here, warrants more attention. Although many previous studies have examined general cognition and the phenomenon of overgeneral memory separately, by combining the two areas any possible links between the various functions may be elucidated. Future research should focus on the processes behind

impaired autobiographical memory recall during the acute phase of depression as well as the lack of consistency in autobiographical memory over time.

Thus far this research has examined the acute effects of depression on cognition and changes to cognition over one year follow-up in healthy controls and depressed participants receiving pharmacotherapy treatment, in a treatment-as-usual longitudinal study. The next section of this study investigates the effect of ECT on cognition in depressed participants randomised to one of two treatment conditions: standard dose bitemporal ECT or high-dose unilateral ECT.

CHAPTER 6: RETROGRADE MEMORY AND COGNITION FOLLOWING HIGH-DOSE UNILATERAL AND STANDARD-DOSE BITEMPORAL ELECTROCONVULSIVE THERAPY-A RANDOMISED CONTROLLED TRIAL

6.1 Introduction

Electroconvulsive therapy (ECT) is a highly effective treatment for depressive illness (UK ECT Review Group, 2003), especially in the case of severe and life-threatening depression and where improvements in the patient's condition are urgently required (National Institute for Clinical Excellence, 2009). However, despite its proven efficacy, ECT remains a somewhat controversial treatment. This controversy is partly due to the fact that, as with many treatments in psychiatry and medicine, the precise mechanism of action of ECT is not yet fully understood (National Institute for Clinical Excellence, 2003). In addition, objective findings as well as subjective complaints of memory dysfunction are common, in particular autobiographical memory loss, after treatment (Rose et al., 2003).

During a session of ECT a current of electricity is passed between electrodes on the patient's scalp to elicit a generalised seizure in the brain (Kellner et al., 2010b). A number of different electrode placement options have been developed for ECT and placements fall into two common categories: bitemporal (BT) ECT and unilateral (UL) ECT. In standard BT ECT an electrode is placed on each temple. For UL ECT electrodes are placed on one side of the head only, usually in the D'Elia position (D'Elia and Raotma, 1975). Electrode placement in UL ECT is usually on the right side of the head, to avoid the occurrence of side-effects to left-hemisphere functions such as language (Kellner et al., 2010b). Seizure threshold (ST), the minimal electrical charge

needed to produce a seizure of adequate clinical duration, may differ across patients and is found by titrating the dose upwards until an adequate seizure occurs (Sackeim et al., 1987). For therapeutic efficacy treatment is given above the ST, usually 1.5 times ST for BT ECT. Research on UL ECT has found low and moderate doses (0.5 to 2.5 times ST) are not as efficacious as BT ECT (Sackeim et al., 1993, Sackeim et al., 2000) but high dose (6 X ST) right UL (RUL) ECT is (Sackeim et al., 2000, Kellner et al., 2010a).

Cognitive side-effects of ECT are often reported, and most research has concentrated on acute and sub-acute effects of ECT, a timeline that ranges from a few days after the final treatment, to two weeks after end of treatment. Fewer studies have investigated longer-term cognitive outcomes after ECT, although this area has been investigated more often only in recent years. Autobiographical memory has consistently been shown to be impaired at end of treatment testing compared to baseline and healthy controls (Sackeim et al., 2007, Sackeim et al., 1993, Sackeim et al., 2000, Sackeim et al., 2008, McCall et al., 2000, Lerer et al., 1995, Calev et al., 1991, Lisanby et al., 2000, Squire et al., 1981). Findings are mixed regarding persisting deficits with some authors reporting no deficit at follow-up (Calev et al., 1991, Lerer et al., 1995)., while others have found impairments up to three years after ECT (Sackeim et al., 2007, Sackeim et al., 2008, Squire and Slater, 1983). With regard to public events memory some have reported deficits at end of treatment compared to baseline performance (Calev et al., 1991, Lerer et al., 1995, Lisanby et al., 2000, Meeter et al., 2011, Sackeim et al., 2000, Sackeim et al., 2008) but no deficits at follow-up (Weiner et al., 1986, Lerer et al., 1995, Meeter et al., 2011). However one study has reported ECT patients as improved in performance on public events memory but still impaired relative to controls at two months follow-up (Lisanby et al., 2000). Mixed findings are reported for general cognitive functions, where no change (Calev et al., 1989, Parker et al., 1993) or small

deficits (Neylan et al., 2001, Sackeim et al., 2007, Tsourtos et al., 2007) have been shown in anterograde memory, attention, psychomotor and executive function after ECT, but may improve to baseline level or above in the long-term (Dubovsky et al., 2001, Ingram et al., 2008, Ng et al., 2000, Sackeim et al., 2007). A number of studies have found that cognitive effects are significantly greater with BT ECT than high-dose RUL ECT post-treatment and up to six months follow-up in retrograde memory and verbal learning (Sackeim et al., 1993, Sackeim et al., 2000, Sackeim et al., 2007, Sackeim et al., 2008).

The aim of the current study was to assess the retrograde memory and general cognitive function of depressed patients randomised to either standard-dose (1.5 X ST) BT ECT or high-dose (6 X ST) RUL ECT at baseline, after a course of ECT, three months and six months later.

Due to the variation in findings from different studies it was difficult to hypothesise as to the effects of ECT on the range of cognitive functions being tested in this study. However, it was hypothesised that patients who received high-dose RUL ECT would experience less retrograde memory and cognitive impairments than those who received standard-dose BT ECT. Based on previous studies (Calev et al., 1991, Lerer et al., 1995, Weiner et al., 1986) it was also hypothesised that autobiographical memory would be worse affected by ECT treatment than public events memory.

6.2 Methods

6.2.1 Ethics and consent

Full ethical approval was granted for this study by the St. Patrick's University Hospital Research Ethics Committee (Protocol number 012/07-Appendix 21) and the St. James's Hospital/Adelaide Meath & National Children's Hospital Research Ethics Committee (Protocol number 2008/05/04- Appendix 22). All participants were given verbal and full written information and asked to provide written informed consent.

6.2.2 Design

The study is a two-group parallel-design randomised controlled non-inferiority trial. The trial is registered with Current Controlled Trials Ltd., trial number: ISRCTN23577151. Consented patients with major depressive disorder (according to Structured Clinical Interview for Axis 1 Disorders (SCID) for the Diagnostic and Statistical Manual of Mental Disorders, Version four (DSM-IV) (American Psychiatric Association, 2000, First et al., 1995)) are randomly allocated to a course of BT ECT (1.5 x ST) or high-dose RUL ECT (6 x ST). To facilitate generalisabilty of results, the trial takes place under "real world" conditions and so both groups continue usual care and medications during treatment phase and thereafter.

In the current study the focus is on a sub-section of data collected as part of the EFFECT-Dep Trial, which examines the effectiveness of ECT in severe depression. In particular, the effect of ECT subtype (BT or UL) on retrospective memory was examined by comparing pre-ECT and post-ECT performance on neuropsychological tests. Recovery of function over time was also examined at three month and six month follow-up.

Randomisation and blinding

Patients were randomised after baseline data collection. Patients and assessors were blind to treatment. Simple random allocation was done independently by the Clinical Trials Unit at the Institute of Psychiatry (London) to help maintain allocation concealment.

Participants

The main entry criterion to the study was being referred for ECT for treatment of a major depressive episode. Patients ≥18 years with major depressive disorder (meeting SCID-I criteria) and referred for ECT were invited to participate. Exclusion criteria included: any condition in which patients were deemed medically unfit for general anaesthesia or ECT; treatment with ECT in previous six months; dementia or other Axis 1 diagnosis; alcohol/other substance abuse in previous six months; inability/refusal to consent.

6.2.3 Procedure

Once a patient met criteria and agreed to enter the trial the baseline assessments were conducted. Any baseline assessments completed had to be carried out prior to the participant undergoing their first ECT treatment. Due to the nature of depressive illness, some participants were unable to complete all assessments at baseline. In such cases, the minimum requirement to enter the study was a completed SCID and Hamilton Depression Rating Scale-24 item (HDRS-24) (Hamilton, 1960, Kovacs et al., 1981). The full assessment battery (Table 55) was again carried out at end of treatment (EOT), which occurred within three days after the patient's final or 12th treatment, and at three month and six month follow-up.

Measure	Baseline	End of Treatment	3 month follow-up	6 month follow-up
ATHF	✓			
SCID-I	✓			
Treatment Review	✓	✓	✓	✓
HDRS[24]	✓	✓	✓	✓
NART	✓			
ACE-R & MMSE	A	B	C	D
AMI-SF	✓	✓	✓	✓
Public Events Questionnaire	✓	✓	✓	✓
Grooved Pegboard	✓	✓	✓	✓
Buschke FCSR	1	2	3	1
ROCF	A	B	C	D
Trail Making Test A & B	✓	✓	✓	✓
Digit Span Forwards & Backwards	I	II	III	I

Table 55 Schedule and list of The EFFECT-Dep Trial assessments

ATHF: Antidepressant Treatment History Form; SCID-I: Structured Clinical Interview DSM-IV, Axis 1; HDRS-24: Hamilton Depression Rating Scale; NART: National Adult Reading Test; ACE-R: Addenbrooke's Cognitive Examination, revised (Parallel versions A,B,C,D); AMI-SF: Autobiographical Memory Interview, Short-form; Buschke Free and Cued Selective Reminding (FCSR) with parallel versions 1, 2 and 3; ROCF: Rey-Osterrieth Complex Figure with parallel versions A, B, C, D; Digit Span (Forwards and Backwards) with parallel versions I, II and III; TMT-A: Trail Making Test Part A; and TMT-B: Trail Making Test Part B.

6.2.4 Data analyses

The EFFECT-Dep trial was run on an intention-to-treat basis, and conducting statistical analyses in this way maintains the benefits of randomisation. Where participants did not complete every assessment over each follow-up data was imputed instead. Imputation was not carried out for the Mem-Dep Study because of a higher amount of missing data. In addition the depressed and control groups in the Mem-Dep Study were designed to be clearly different, and therefore differences were likely to be found if present, despite the small sample. Patterns of missing data were analysed to determine if data was missing completely at random (MCAR), whereby missing data is not related to either the independent or dependent variables, or missing at random (MAR), where missing data may be related to the independent variables but not the dependent variables (Shaughnessy et al., 2003). Missing data were imputed using estimation-maximisation (EM) methods using the Statistics Package for Social Science (SPSS) version 16 (SPSS Inc., 2009) Missing Values Analysis command. The EM method obtains maximum likelihood estimates of the missing data and is suitable for use with MAR data (Shaughnessy et al., 2003).

Results are presented as mean (M) and standard deviation (SD). Independent t-tests were used to identify any baseline differences between participants in the UL and BT ECT groups. Non-parametric alternatives (Mann-Whitney U tests) were used where data were not normally distributed. Longitudinal data were analysed using mixed between-within ANOVA's with Bonferroni post-hoc tests. This type of ANOVA examines main effects where one independent variable is between groups (i.e. participant group, Right UL or BT ECT), and one independent variable is within groups (time of assessment) (Pallant, 2007). Where significant effects were found within groups additional one-way repeated measures ANOVA's were conducted to find where

the differences lay within each group. Where significant differences were found between groups independent t-tests (or non-parametric alternatives) were used to pinpoint which time-periods differed. Effect-sizes were estimated using partial eta-squared, as recommended for mixed between-within ANOVA's (Pallant, 2007, Conway and Pleydell-Pearce, 2000). Partial eta-squared statistics are variance based effect-sizes and explain what proportion of the variance in the dependent measure is attributable to the independent variable. All data were analysed using SPSS version 16 (SPSS Inc., 2009).

6.3 Results

At baseline 86 participants had been recruited (Figure 48) and completed assessments prior to receiving ECT treatment and were randomised to the standard-dose BT ECT or the high-dose RUL ECT. These 86 individuals were the first 86 participants to be recruited into the EFFECT-Dep Trial. Power analysis for the EFFECT-Dep trial had previously indicated that 138 participants would be necessary in the trial (69 per treatment arm) for adequate power to detect differences between the two ECT treatment groups. As such the results of the first 86 participants reported here are preliminary, not definitive and may not reflect the final outcomes of the completed trial.

Of the first 86 trial participants 81.4% were referred for treatment resistant depression (unipolar and bipolar), 9.3% for treatment of severe depression and 9.3% for treatment of psychotic depression. Differences in background factors including age, gender, education, National Adult Reading Test (NART) scores (Nelson and Willison, 1991), HDRS-24 scores, previous ECT and treatment resistance were assessed (ATHF (Oquendo et al., 1999, Sackeim et al., 1990), Table 56). No significant differences were found between the BT ECT and RUL ECT groups for any cognitive measure, however there was a significant difference between levels of education attainment, with the BT ECT group having fewer participants with secondary and tertiary education and more participants with quaternary education than the RUL ECT group (Table 56). Differences between those who had been treated with ECT on one or more previous occasions and those who had no history of ECT were also assessed. A significant difference was found between these groups for performance on the MMSE and on the Grooved Pegboard Test (Table 56).

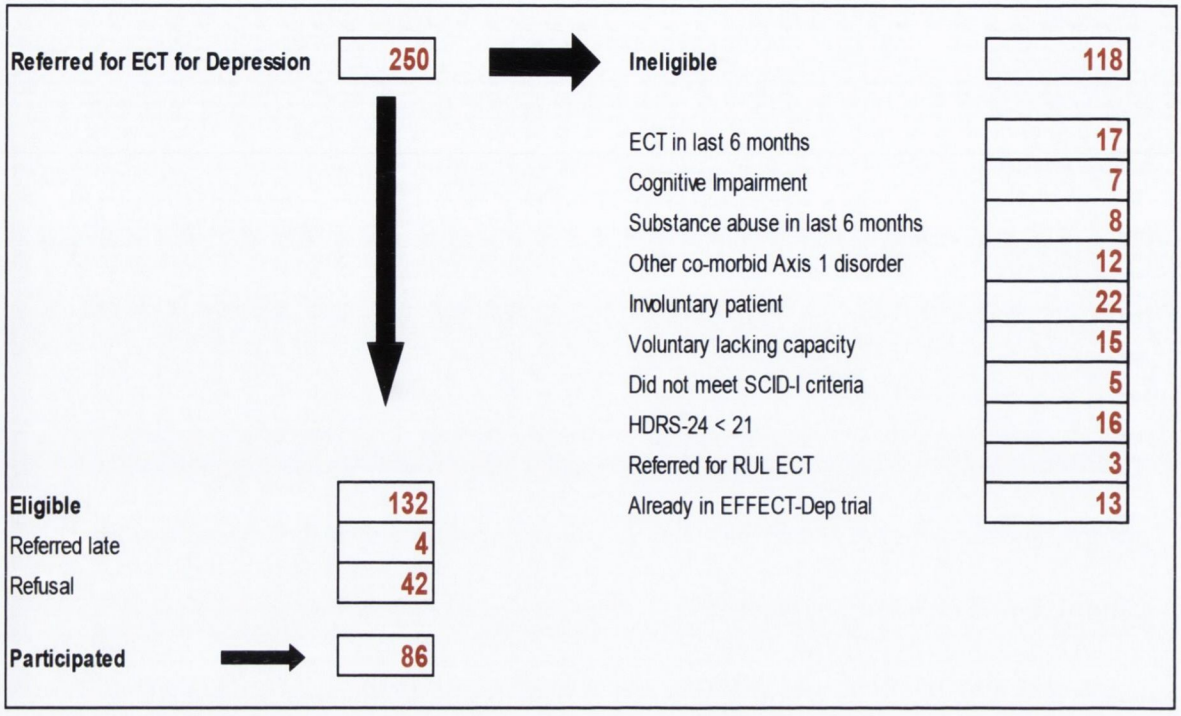


Figure 48 Recruitment for the EFFECT-Dep Trial from May 2008 to September 2010

Measure/ characteristic	RUL ECT	BT ECT	Test Statistic		
	n=43	n=43	t (d.f.)	$\chi 2$ (d.f.)	p value
Age-years, mean (s.d.)	56.19 (15.2)	59.49 (13.3)	-1.075 (84)		0.286
Female (%)	25 (58)	25 (58)		<0.001(1)	1.000
NART, mean (s.d.)	108.32 (5.2)	107.50 (7.7)	0.580 (84)		0.564
HDRS-24, mean (s.d.)	31.23 (6.8)	29.47 (7.2)	-1.527 (84)		0.127
Previous ECT	19 (44)	19 (44)		<0.001 (1)	1.000
Treatment resistant n (%)	23 (53.5)	26 (60.5)			
Education level, n (%)	*n=43*	*n=41*			
• Primary	2 (4.6)	9 (21.9)		12.124 (3)	0.007
• Secondary	27 (62.8)	22 (53.7)			
• Tertiary	14 (32.6)	6 (14.6)			
• Quaternary	0 (0)	4 (9.8)			
Measure/ characteristic	**Previous ECT**	**No previous ECT**	**Test Statistic**		
	n=39	n=47	z score		p value
MMSE	26.79 (1.7)	27.97 (2.1)	-3.673		0.000
Grooved Pegboard Test	144.74 (32.2)	124.86 (39.7)	-2.566		0.010

Table 56 Baseline characteristics of ECT groups

6.3.1 Cognitive changes from baseline to six month follow-up

Performance of the EFFECT-Dep Trial participants was analysed using mixed plot ANOVA's, examining main effects within groups over time, between groups and the interaction between time and group. Data did not meet the assumptions of multicollinearity and singularity necessary for multivariate analyses and for this reason univariate analyses, where each assessment measure was analysed separately, were conducted for all measures and a more stringent significance value of $p<0.01$ was adopted for all analyses to control for effects of multiple testing. Significant main effects were investigated further using repeated measures ANOVA and independent t-tests respectively and effect-sizes were estimated using partial eta-squared.

Clinical variables were not analysed using ANOVA's as the EFFECT-Dep Trial is on-going and efficacy of BT ECT and RUL ECT in the current study cannot be determined until the trial has concluded. As such the findings reported here are for the purposes of this thesis only and may not represent the final outcome of the EFFECT-Dep Trial. However, to relate the changes in cognitive function over time to changes in depression severity a series of Pearson's product moment correlations (or non-parametric alternative) were conducted between the HDRS-24 and each cognitive measure at each time-point.

6.3.1.1 Global cognitive function

No significant interaction was found for performance on the ACE-R at EOT, three and six month follow-up from baseline between group and time, nor was a significant difference found between groups. There was a significant change within groups over time, and further analyses indicated that both the RUL ECT and the BT ECT groups changed over time (Table 57). In the RUL ECT group performance on the

ACE-R was significantly higher at six months follow-up than baseline and EOT. In the BT ECT group performance at EOT was significantly lower than all other times, while performances at both three and six month were also significantly better than at baseline (Figure 49).

No significant interaction was found on the MMSE between group and time. No significant differences were found between groups and there was no significant change in scores over time (Table 58, Figure 50).

Addenbrooke's Cognitive Examination-Revised

Time	High-dose RUL ECT n=43	Standard BT ECT n=43	Comparison	F (d.f.)	p value	Effect-size
Baseline	81.35 (9.8)	79.11 (9.8)				
E.O.T	79.91 (11.8)	75.11 (11.7)	Group	1.578 (1)	0.213	0.018
3 months	84.03 (10.0)	83.13 (7.2)	Time	13.42 (3)	<0.001	0.329
6 months	85.12 (9.0)	84.24 (8.0)	Group*Time	1.121 (3)	0.308	0.043

Table 57 Addenbrooke's Cognitive Examination-Revised: means (SD) over six month follow-up

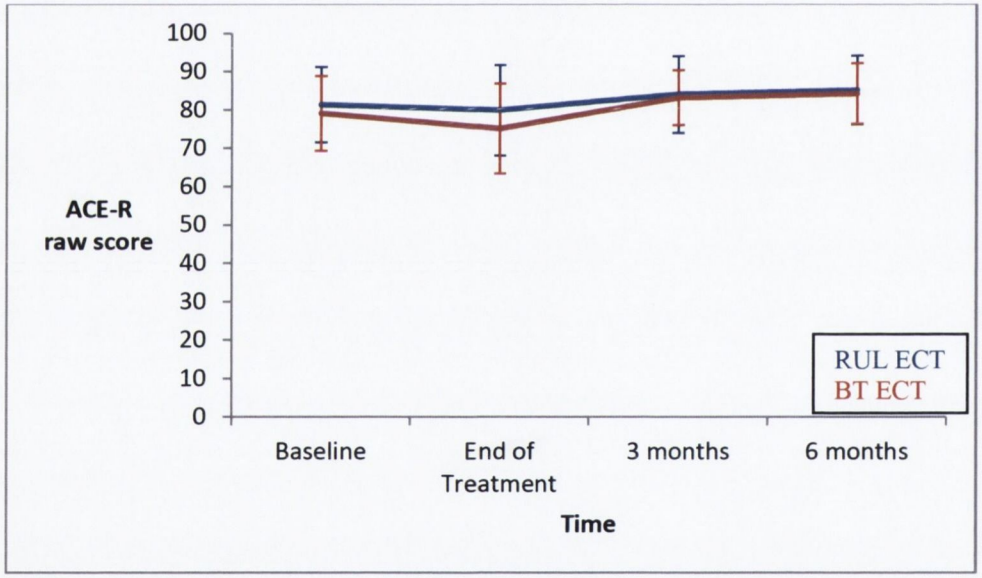


Figure 49 Addenbrooke's Cognitive Examination-Revised: means (SD) over six month follow-up

Mini Mental State Examination

Time	High-dose RUL ECT n=43	Standard BT ECT n=43	Comparison	F (d.f.)	p value	Effect-size
Baseline	27.47 (2.2)	27.40 (1.8)				
E.O.T	27.41 (2.7)	26.62 (2.7)	Group	0.318 (1)	0.575	0.004
3 months	27.66 (2.0)	27.84 (1.3)	Time	2.415 (3)	0.072	0.081
6 months	27.60 (2.4)	27.51 (2.1)	Group*Time	1.046 (3)	0.377	0.037

Table 58 Mini Mental State Examination: means (SD) over six month follow-up

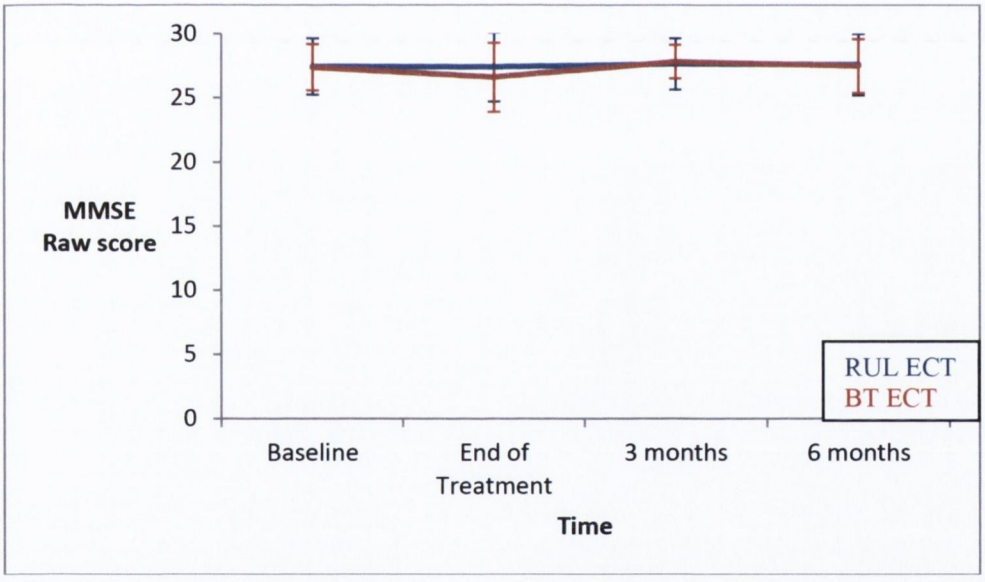


Figure 50 Mini Mental State Examination: means (SD) over six month follow-up

6.3.1.3 Retrograde amnesia

Original raw scores at baseline on the AMI-SF were converted to percentages, with the details provided by both groups representing 100%. Consistency of follow-up recall with baseline was then assessed at EOT, three and six months follow-up. The interaction between group and time was not significant and there was no significant difference between groups on the AMI-SF, although this difference did approach significance ($p=0.020$). Within groups over time there was a significant change in performance on the AMI-SF (Table 59). Post-hoc tests indicated that scores changed significantly for both groups, with all follow-up times being significantly lower than baseline in both groups ($p<0.001$, Figure 51).

No significant interaction was found between group and time on the Public Events Questionnaire, although the difference approached significance (Table 60). No significant differences were found for performance on the Public Events Questionnaire between groups. Within groups there was a significant change in performance on the Public Events Questionnaire, and post-hoc tests indicated that this effect was in the BT ECT group only, where performance at EOT was significantly lower than at all other assessment points (Figure 52).

Autobiographical Memory Interview (Short-form)

Time	High-dose RUL ECT n=43	Standard BT ECT n=43	Comparison	F (d.f.)	p value	Effect-size
Baseline	100.00 (0.0)	100.00 (0.0)				
E.O.T	67.48 (16.8)	61.12 (16.6)	Group	5.651	0.020	0.063
3 months	66.00 (12.0)	60.26 (15.9)	Time	2.879 (3)	<0.001	0.913
6 months	65.03 (13.5)	58.57 (12.8)	Group*Time	2.004 (3)	0.120	0.068

Table 59 Autobiographical Memory Interview (Short-form): means (SD) over six month follow-up

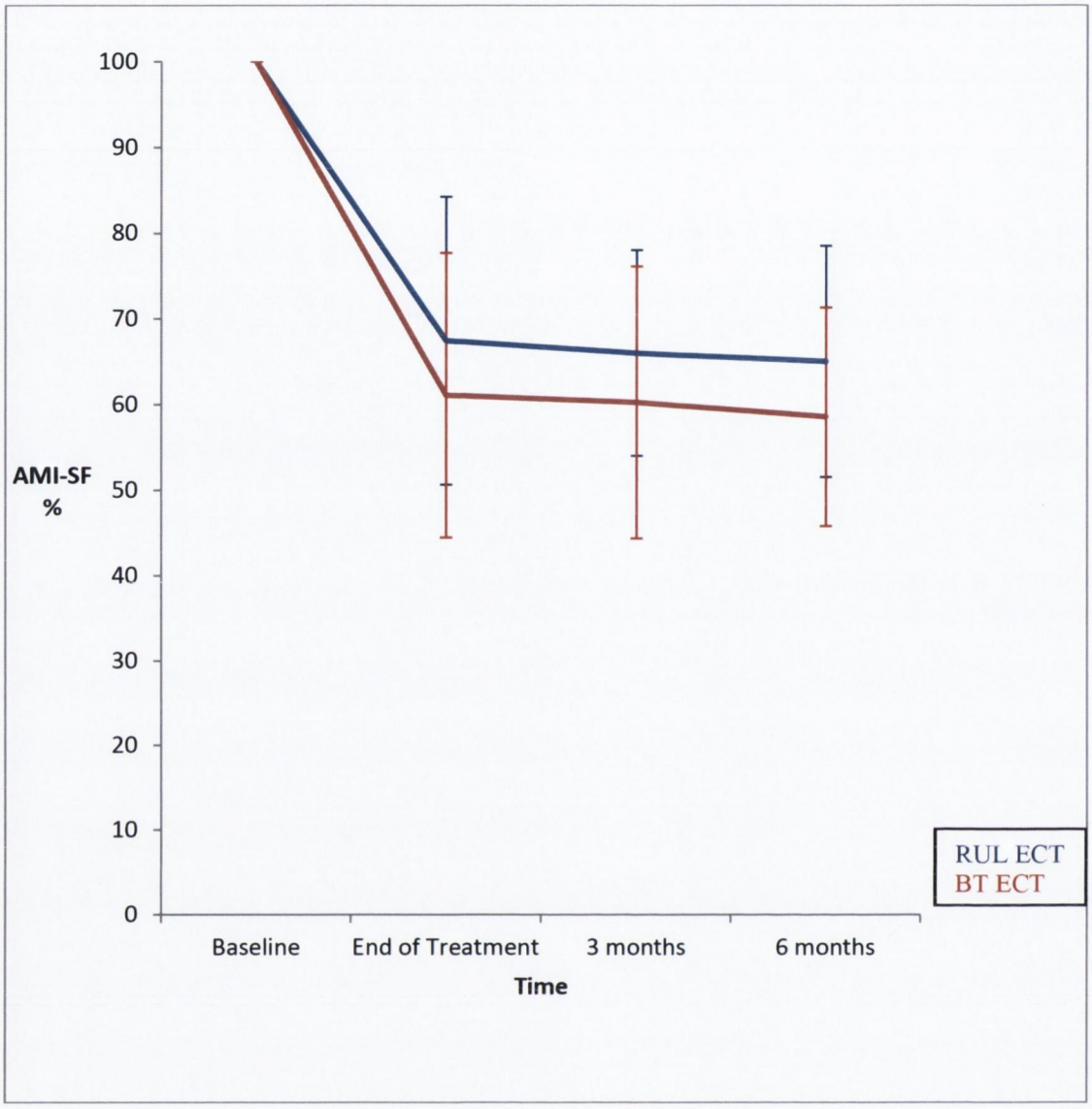


Figure 51 Autobiographical Memory Interview (Short-form): means (SD) over six month follow-up

Public Events Questionnaire

Time	High-dose RUL ECT n=43	Standard BT ECT n=43	Comparison	F (d.f.)	p value	Effect-size
Baseline	64.26 (21.9)	60.66 (19.6)				
E.O.T	63.47 (22.8)	50.11 (18.2)	Group	2.447 (1)	0.122	0.028
3 months	67.13 (20.8)	63.28 (16.2)	Time	10.107(3)	<0.001	0.270
6 months	68.32 (18.7)	66.94 (16.5)	Group*Time	3.708 (3)	0.015	0.119

Table 60 Public Events Questionnaire: means (SD) over six month follow-up

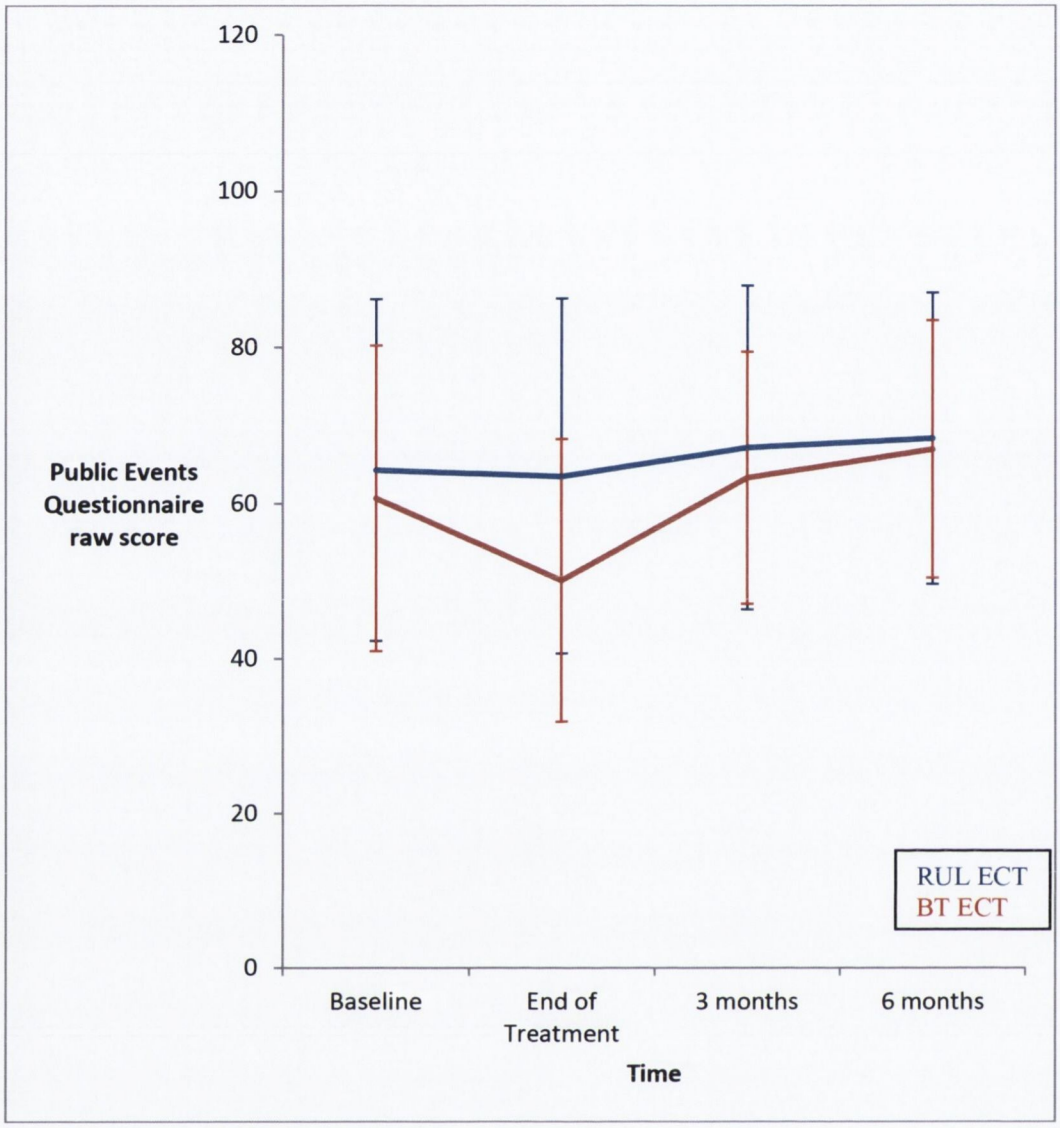


Figure 52 Public Events Questionnaire: means (SD) over six month follow-up

6.3.1.4 Anterograde verbal learning and memory

No significant interaction was found between group and time on the Buschke FCSR immediate recall task and no difference was found between groups (Table 61). Within groups there was a significant change in performance over time, and post-hoc tests indicated that this effect was in the BT ECT group only. In the BT ECT group performance at EOT was significantly lower than at three and six month follow-up. In addition performance at three months was significantly higher than baseline (Figure 53).

Similarly, no significant interaction was found between group and time on the Buschke FCSR free delayed recall task (Table 62). No significant differences were found for performance between groups either. Within groups there was a significant change in performance on the delayed recall task over time, and again this effect was seen in the BT ECT group only, where performance at EOT was significantly lower than at all other assessment points (Figure 54).

Buschke FCSR Immediate recall

Time	High-dose RUL ECT n=43	Standard BT ECT n=43	Comparison	F (d.f.)	p value	Effect-size
Baseline	23.52 (6.8)	22.48 (7.8)				
E.O.T	22.55 (9.4)	20.10 (8.4)	Group	0.303 (1)	0.584	0.004
3 months	25.35 (6.5)	25.65 (5.6)	Time	9.520 (3)	<0.001	0.258
6 months	24.64 (6.6)	25.11 (6.1)	Group*Time	0.996 (3)	0.399	0.035

Table 61 Buschke FCSR Immediate recall: means (SD) over six month follow-up

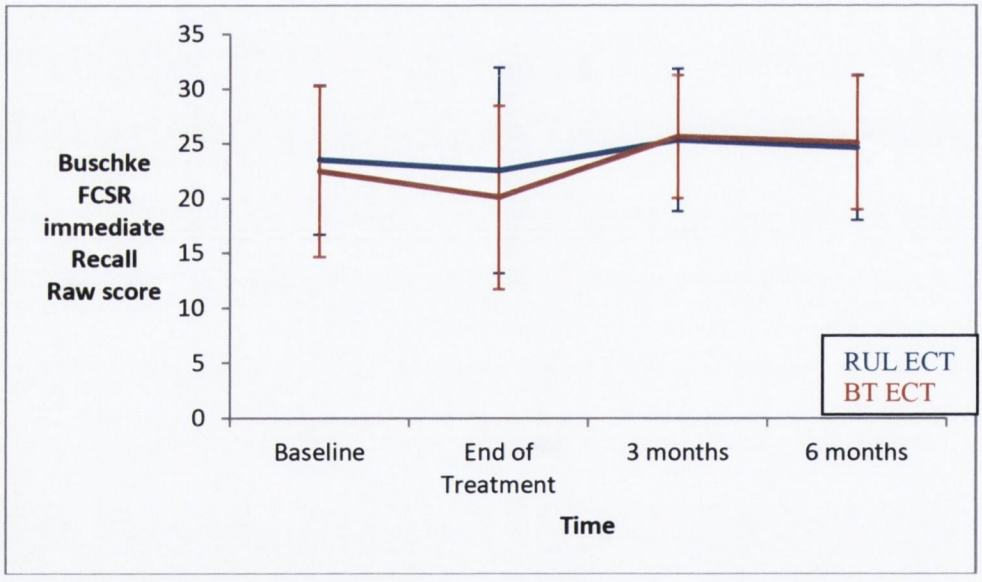


Figure 53 Buschke FCSR Immediate recall: means (SD) over six month follow-up

Buschke Free Delayed Recall

Time	High-dose RUL ECT	Standard BT ECT	Comparison	F (d.f.)	p value	Effect-Size
Baseline	9.26 (2.9)	8.54 (3.2)				
E.O.T	8.23 (2.6)	6.94 (3.2)	Group	1.856 (1)	0.177	0.022
3 months	8.87 (2.3)	8.83 (2.1)	Time	7.494 (3)	<0.001	0.215
6 months	9.18 (2.6)	8.84 (2.3)	Group*Time	1.333 (3)	0.269	0.047

Table 62 Buschke FCSR delayed recall: means (SD) over six month follow-up

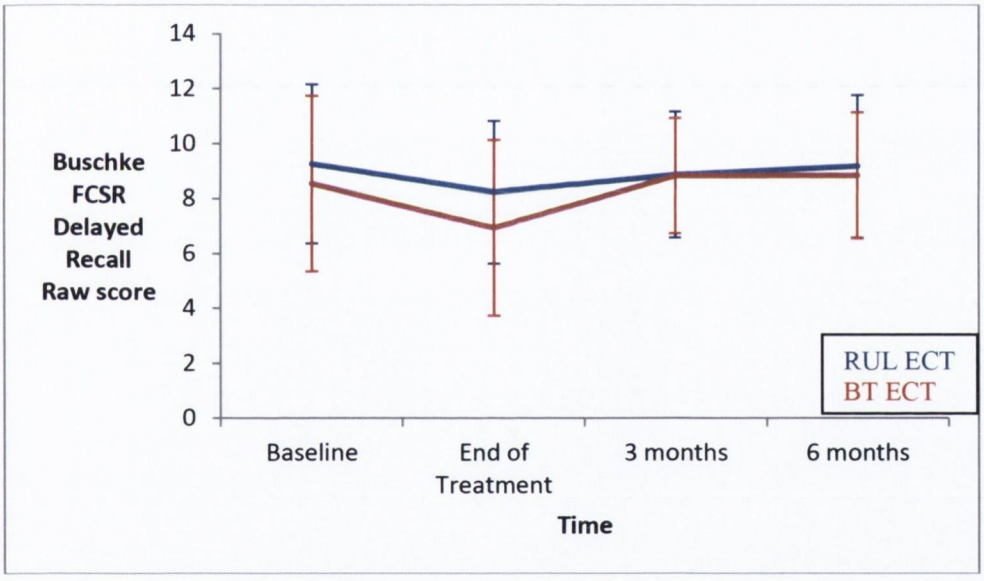


Figure 54 Buschke FCSR delayed recall: means (SD) over six month follow-up

6.3.1.5 Anterograde visual learning and memory

No significant interaction was found between group and time on the ROCF immediate recall task and no difference was found between groups (Table 63). Within groups there was a significant change in performance over time in both groups. In the RUL ECT group performance at baseline was significantly lower than at all other times. In addition performance at six months was significantly better than EOT. In the BT ECT group performances at baseline and EOT were significantly lower than at both three and six month follow-up (Figure 55).

Similarly, no significant interaction was found between group and time on the ROCF delayed recall task (Table 64). No significant differences were found for performance between groups either. Within groups there was a significant change in performance over time in both groups. In the both groups performance at baseline was significantly lower than at all other assessment points and performance at EOT was significantly lower than three and six months (Figure 56).

Rey-Osterreith Complex Figure immediate recall

Time	High-dose RUL ECT	Standard BT ECT	Comparison	F (d.f.)	p value	Effect-Size
Baseline	10.43 (5.8)	8.98 (6.0)				
E.O.T	13.71 (6.8)	11.54 (8.2)	Group	1.411 (1)	0.238	0.017
3 months	16.25 (8.0)	14.82 (5.9)	Time	36.068(3)	<0.001	0.569
6 months	17.08 (7.8)	16.21 (5.9)	Group*Time	0.282 (3)	0.838	0.010

Table 63 Rey-Osterreith Complex Figure immediate recall: means (SD) over six month follow-up

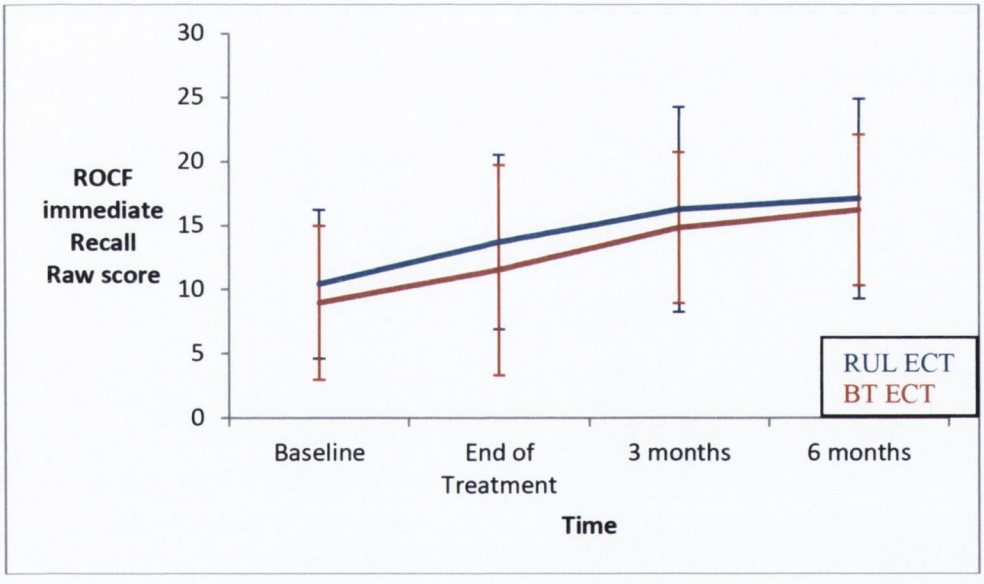


Figure 55 Rey-Osterreith Complex Figure immediate recall: means (SD) over six month follow-up

Rey-Osterrieth Complex Figure delayed recall

Time	High-dose RUL ECT n=43	Standard BT ECT n=43	Comparison	F (d.f.)	p value	Effect-Size
Baseline	9.36 (6.2)	7.85 (6.6)				
E.O.T	12.46 (6.9)	10.68 (8.6)	Group	1.079 (1)	0.302	0.013
3 months	15.37 (7.1)	14.44 (5.6)	Time	39.32 (3)	<0.001	0.590
6 months	16.34 (7.7)	15.40 (5.7)	Group*Time	0.141 (3)	0.935	0.005

Table 64 Rey-Osterreith Complex Figure delayed recall: means (SD) over six month follow-up

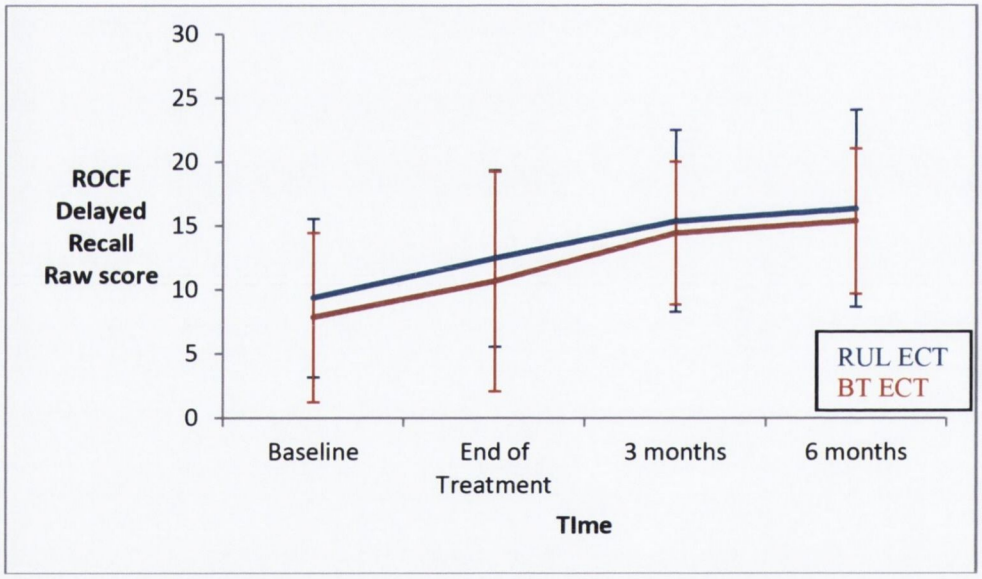


Figure 56 Rey-Osterreith Complex Figure delayed recall: means (SD) over six month follow-up

6.3.1.7 Attention and working memory

No significant interaction was found between group and time on the Digit Span Forwards task. A significant difference was found between groups on this task (Table 65) and further analyses indicated that the difference between groups at six months follow-up approached significance ($z=-2.422$, $p=0.015$, Figure 57). Within groups there was a significant change in performance over time in the RUL ECT group only. In the RUL ECT group performance at EOT was significantly better than baseline and 3 months follow-up.

No significant interaction was found between group and time on the Digit Span Backwards task. No significant differences were found for performance between groups or within groups over time, although the change over time approached significance (Table 66, Figure 58).

Digit Span Forwards

Time	High-dose RUL ECT n=43	Standard BT ECT n=43	Comparison	F (d.f.)	p value	Effect-Size
Baseline	8.00 (2.7)	7.24 (2.3)				
E.O.T	9.23 (2.5)	8.11 (2.1)	Group	6.875 (1)	0.010	0.076
3 months	8.13 (1.9)	7.49 (1.3)	Time	9.060 (3)	<0.001	0.249
6 months	8.93 (2.2)	7.91 (1.5)	Group*Time	0.502 (3)	0.682	0.018

Table 65 Digit Span Forwards: means (SD) over six month follow-up

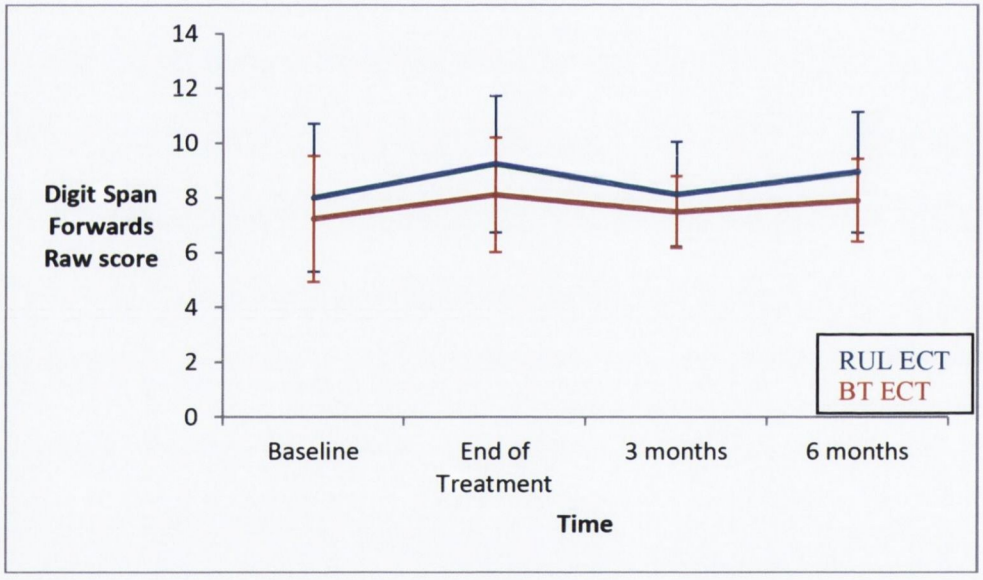


Figure 57 Digit Span Forwards: means (SD) over six month follow-up

Digit Span Backwards

Time	High-dose RUL ECT n=43	Standard BT ECT n=43	Comparison	F (d.f.)	p value	Effect-Size
Baseline	5.34 (2.0)	5.19 (1.9)				
E.O.T	5.47 (2.5)	4.99 (2.4)	Group	0.963 (1)	0.329	0.011
3 months	5.73 (1.5)	5.41 (1.3)	Time	3.884 (3)	0.012	0.124
6 months	6.17 (2.2)	5.89 (1.5)	Group*Time	0.214 (3)	0.887	0.008

Table 66 Digit Span Backwards: means (SD) over six month follow-up

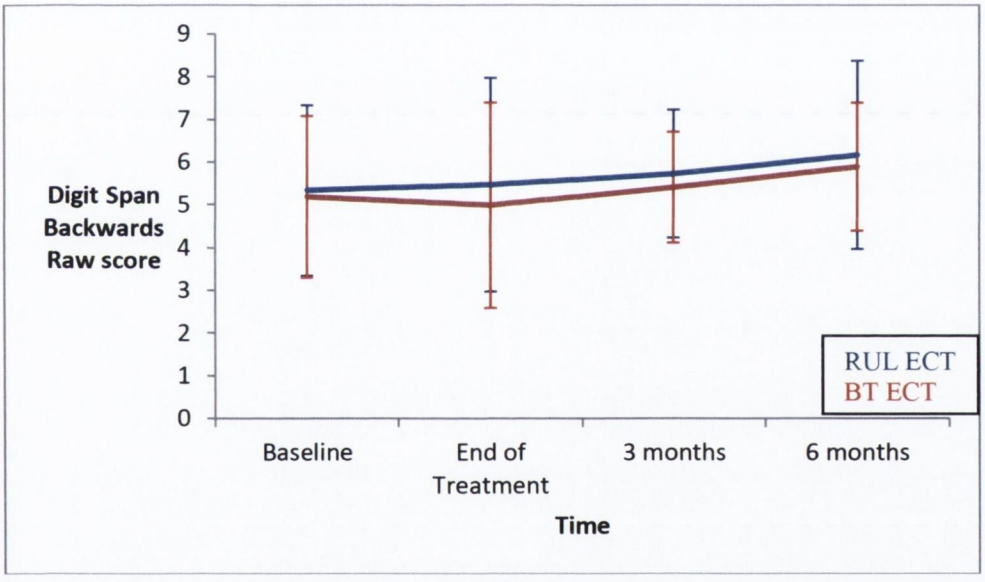


Figure 58 Digit Span Backwards: means (SD) over six month follow-up

6.3.1.9 Psychomotor speed and processing

No significant interaction was found between group and time on the Grooved Pegboard Test, and no significant difference was found between groups. Within groups there was a significant change in performance over time in both groups. In the RUL ECT group performance improved significantly from baseline to EOT and from baseline to three month follow-up. In the BT ECT group performance showed significant improvement at three and six months follow-up compared to baseline (Table 67, Figure 59).

No significant interaction was found between group and time on the Trail Making Test A, and there was no significant difference found between groups. Within groups there was a significant change in performance over time. When groups were analysed separately this effect was not found to be significant in the RUL ECT group and only approached significance in the BT ECT group ($p=0.011$), where baseline performance was worse than performance at three and six months (Table 68, Figure 60).

Grooved Pegboard Test

Time	High-dose RUL ECT n=43	Standard BT ECT n=43	Comparison	F (d.f.)	p value	Effect-Size
Baseline	131.87 (38.1)	135.87 (37.5)				
E.O.T	117.87 (38.4)	126.82 (34.7)	Group	0.320 (1)	0.573	0.004
3 months	115.07 (30.0)	113.94 (27.6)	Time	0.614 (3)	<0.001	0.257
6 months	117.83 (30.0)	118.74 (24.5)	Group*Time	0.614	0.608	0.022

Table 67 Grooved Pegboard Test: means (SD) over six month follow-up

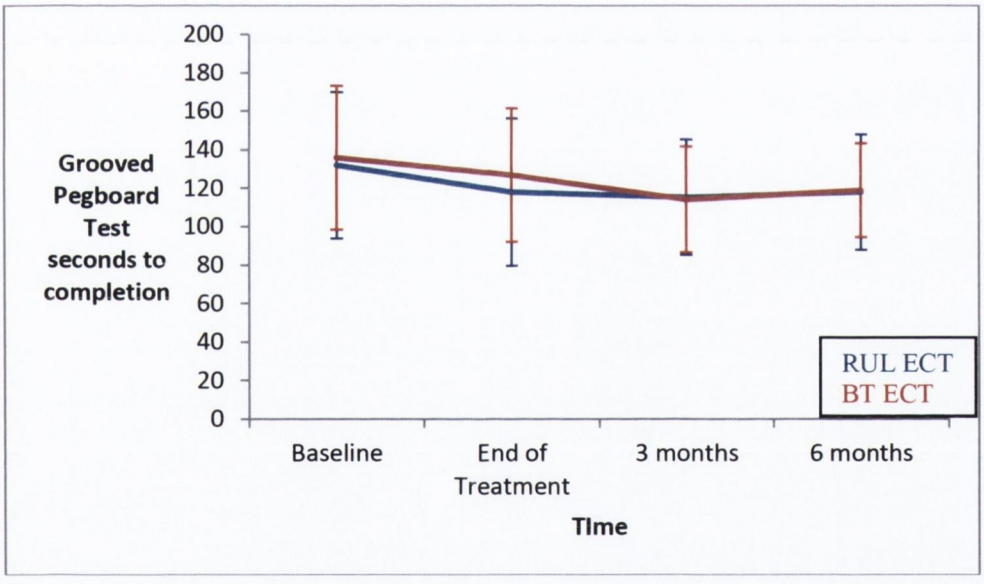


Figure 59 Grooved Pegboard Test: means (SD) over six month follow-up

Trail Making Test A

Time	High-dose RUL ECT n=43	Standard BT ECT n=43	Comparison	F (d.f.)	p value	Effect-Size
Baseline	62.20 (25.7)	72.43 (35.4)				
E.O.T	77.99 (61.6)	65.10 (35.7)	Group	0.076 (1)	0.784	0.001
3 months	54.46 (17.3)	53.29 (20.1)	Time	6.965 (3)	<0.001	0.203
6 months	57.47 (34.6)	55.14 (21.9)	Group*Time	2.999 (3)	0.035	0.099

Table 68 Trail Making Test A: means (SD) over six month follow-up

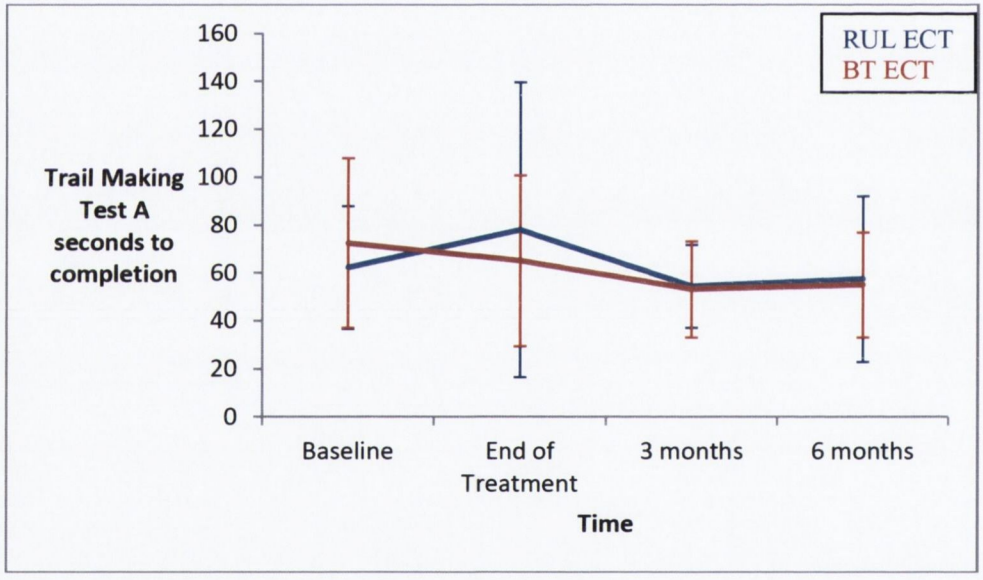


Figure 60 Trail Making Test A: means (SD) over six month follow-up

6.3.1.10 Executive function

No significant interaction was found between group and time on the Trail Making Test B, and no significant difference was found between groups. Within groups there was a significant change in performance over time in both groups. In the RUL ECT group performance at baseline was significantly worse than three month follow-up. In the BT ECT group performance at baseline was significantly worse than three and six months follow-up and performance at EOT was significantly worse than three month follow-up (Table 69, Figure 61).

No significant interaction was found between group and time on the Category fluency task, and no significant difference was found between groups. Within groups there was a significant change in performance over time in both groups. In the RUL ECT group performance at EOT was significantly worse than three and six month follow-up. In the BT ECT group performance at EOT was also significantly worse than three and six months follow-up (Table 70, Figure 62).

No significant interaction was found between group and time on the Letter fluency task, and no significant difference was found between groups. Within groups there was again a significant change in performance over time in both groups. In the RUL ECT group performance at EOT was significantly worse than three and six month follow-up. In the BT ECT group performance at EOT was significantly worse than three months follow-up and performance at three months was significantly worse than that at six months follow-up (Table 71, Figure 63).

Trail Making Test B

Time	High-dose RUL ECT n=43	Standard BT ECT n=43	Comparison	F (d.f.)	p value	Effect-Size
Baseline	174.82 (100.4)	181.83 (100.3)				
E.O.T	157.90 (94.4)	160.68 (81.6)	Group	0.007 (1)	0.935	0.000
3 months	124.75 (58.7)	122.52 (50.3)	Time	12.419(3)	<0.001	0.312
6 months	137.53 (92.5)	134.75 (64.1)	Group*Time	0.093 (3)	0.964	0.003

Table 69 Trail Making Test B: means (SD) over six month follow-up

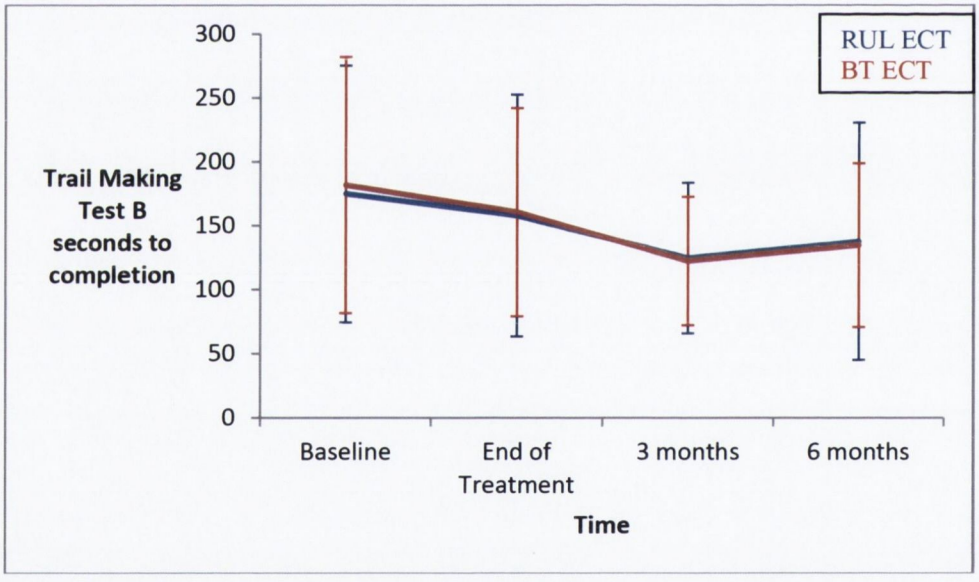


Figure 61 Trail Making Test B: means (SD) over six month follow-up

Category Fluency

Time	High-dose RUL ECT n=43	Standard BT ECT n=43	Comparison	F (d.f.)	p value	Effect-Size
Baseline	14.16 (5.4)	12.98 (4.9)				
E.O.T	12.31 (4.8)	11.05 (5.7)	Group	1.548 (1)	0.217	0.018
3 months	14.47 (4.4)	14.08 (5.4)	Time	10.053(3)	<0.001	0.269
6 months	15.20 (4.6)	13.74 (4.3)	Group*Time	0.630 (3)	0.598	0.023

Table 70 Category fluency: means (SD) over six month follow-up

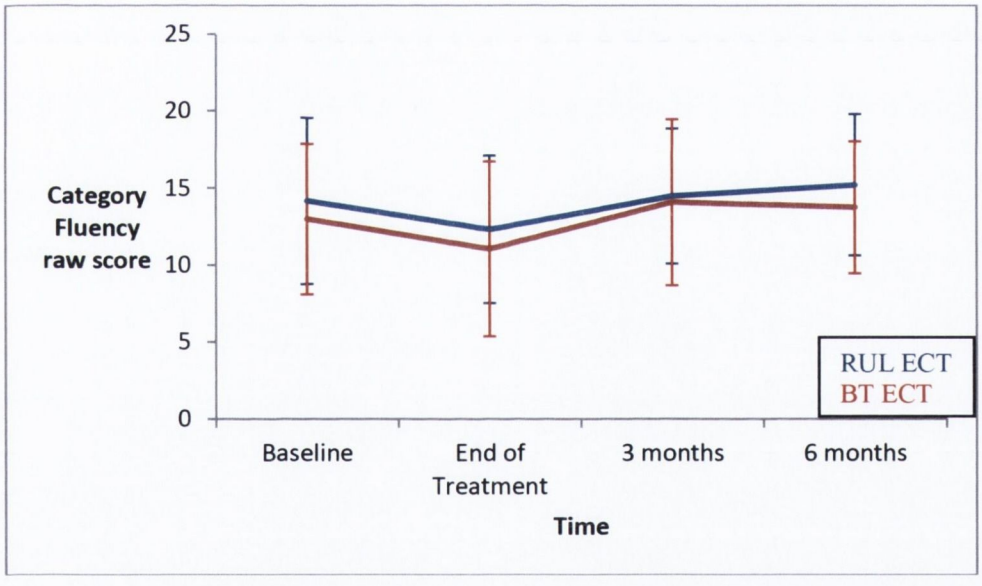


Figure 62 Category fluency: means (SD) over six month follow-up

Letter fluency

Time	High-dose RUL ECT n=43	Standard BT ECT n=43	Comparison	F (d.f.)	p value	Effect-Size
Baseline	11.34 (5.1)	11.26 (4.5)				
E.O.T	9.74 (5.0)	10.12 (4.1)	Group	<0.001(1)	0.984	<0.001
3 months	11.91 (4.9)	11.65 (4.0)	Time	12.459(3)	<0.001	0.313
6 months	12.98 (4.7)	13.00 (3.5)	Group*Time	0.164 (3)	0.921	0.006

Table 71 Letter fluency: means (SD) over six month follow-up

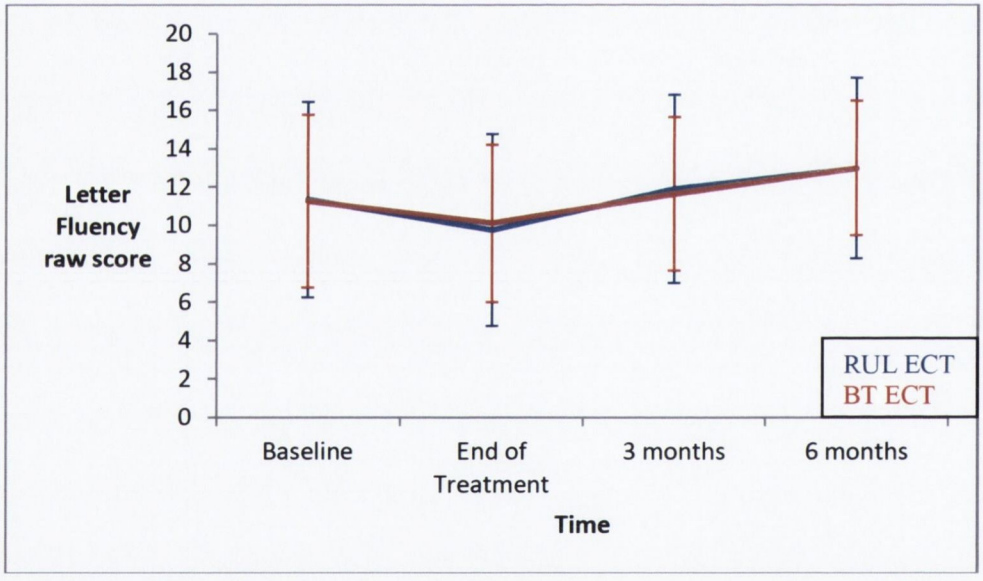


Figure 63 Letter fluency: means (SD) over six month follow-up

6.3.1.11 Summary of cognitive findings

In terms of global clinical functioning, there was no difference between groups on the ACE-R or MMSE. Both groups changed significantly across time on the ACE-R, with those in the RUL ECT group showing a significant increase in performance at three and six month compared to baseline and EOT. The BT ECT group also showed a significant increase in performance at three and six month compared to baseline, and performance at EOT was significantly lower than all other times.

In terms of retrograde memory, the difference between groups approached, but did not reach significance on the AMI-SF, with the RUL group performing better at all times. Both groups performed significantly lower than baseline at all follow-up assessments, and became less consistent at recalling memories at each subsequent time-point. At six months follow-up the RUL group recalled 65% of memories provided at baseline and the BT ECT group recalled 59% of memories consistent with baseline. There was no difference between groups on the Public Events Questionnaire. Over time the BT ECT group performed significantly lower at EOT than all other times, but there was no significant difference between time-periods for the RUL ECT group.

With regard to anterograde verbal learning and memory, no differences were found between groups for either the immediate recall or delayed free recall task on the Buschke FCSR. The BT ECT group changed significantly over time on the immediate recall task, where performance was worst at EOT, but improved significantly from EOT at three and six months follow-up. In addition three month performance was significantly better than baseline. There was no significant difference over follow-up in the RUL ECT group. Similarly the BT ECT group showed significant change over time on the delayed recall task, where performance at EOT was significantly worse than all other time-points.

Performance on both the ROCF immediate and delayed recall tasks was not different between RUL and BT ECT groups. On the immediate recall task the UL group performed significantly worse at baseline compared to all other times, and six month performance was significantly better than EOT. In the BT ECT group both baseline and EOT performance was significantly worse than three and six month performance. For the delayed task, both groups again showed significant increase in scores over time, with both groups performing significantly lower at baseline than all other times, and significantly lower at EOT than at three and six month follow-up.

Regarding attention, there was a significant main effect between groups on the Digit Span Forwards. Further analysis showed that this effect approached significance at six month follow-up ($p=0.015$) and the RUL group performed better at all times. Over time a significant change was observed in the RUL group only, where performance was significantly better at EOT than baseline and three months. There were no differences between or within groups on the Digit Span Backwards.

With regard to psychomotor function, there was no difference between treatment groups on the Grooved Pegboard Test or the TMT-A. Both groups showed significant changes over time on the Grooved Pegboard Test, with the RUL group performing significantly worse at baseline than EOT and three months, and the BT group performing significantly worse at baseline and at EOT compared to three and six months follow-up. Performance on the TMT-A approached significance for the BT ECT group only, where performance at baseline was worse than at three and six months follow-up.

Finally the executive functions were examined and there were no differences between groups on the TMT-B, category fluency and letter fluency tests. For the TMT-B both groups changed significantly over time with the RUL ECT group significantly

improved at three months compared to baseline and EOT and the BT ECT group significantly improved at three months compared to baseline and EOT, and at six months compared to baseline. For category fluency both groups performed significantly worse at EOT compared to three and six months follow-up. For letter fluency the RUL ECT group performed significantly worse at EOT than three and six months, whereas the BT ECT group performed significantly worse at EOT than three months and at three months compared to six months follow-up.

6.3.2 Correlations between depression severity and cognitive function

Correlations were carried out between each cognitive measure and the HDRS-24 at each time-point to investigate the relationship between depression severity and cognitive function (Table 72). As data on the HDRS-24 was not normally distributed Spearman's Rho was used in these analyses as a non-parametric alternative to Pearson's Product-moment correlation. Participants from the RUL ECT and BT ECT groups were combined for these analyses. Due to the high number of comparisons carried out a more stringent significance value ($p<0.01$) was adopted.

There were no significant correlations with the HDRS-24 at baseline. At EOT a higher score on the ROCF immediate recall and delayed recall tasks was significantly related to increased depression severity. At the same time-point the correlation between the HDRS-24 and both the Buschke FCSR immediate and delayed recall tasks approached significance, again with a higher score being linked to more severe depression. No significant correlations were found at three month follow-up. Finally, worse performance on the Grooved Pegboard Test was found to correlate significantly with higher scores on the HDRS-24 at six month follow-up.

Measure	Baseline		End of Treatment		3 Months		6 Months	
	rho	p	rho	p	rho	p	rho	p
ACE-R	0.062	0.571	0.075	0.495	0.115	0.293	-0.110	0.313
MMSE	-0.089	0.416	0.133	0.222	0.056	0.607	-0.113	0.301
AMI-SF	0.035	0.751	-0.124	0.256	-0.083	0.449	-0.074	0.501
Public Events Questionnaire	-0.132	0.226	0.158	0.147	0.153	0.160	-0.002	0.983
Buschke FCSR immediate recall	0.161	0.138	0.272	0.011*	-0.043	0.692	0.143	0.190
Buschke FCSR delayed recall	0.091	0.405	0.236	0.029*	0.000	0.997	0.008	0.940
ROCF Immediate recall	-0.083	0.446	0.297	0.005**	0.047	0.664	-0.084	0.440
ROCF delayed recall	0.032	0.767	0.336	0.002**	0.168	0.122	-0.039	0.723
Digit Span Forward	0.072	0.511	0.027	0.805	-0.096	0.379	-0.120	0.271
Digit Span Backward	0.043	0.693	0.036	0.744	0.143	0.190	-0.115	0.292
Grooved Pegboard Test	0.018	0.872	-0.134	0.219	-0.139	0.202	-0.361	0.001**
TMT-A	-0.025	0.819	-0.196	0.070	-0.166	0.126	-0.009	0.936
TMT-B	-0.073	0.503	-0.167	0.124	-0.088	0.421	-0.017	0.875
Category fluency	0.000	0.999	0.146	0.181	0.060	0.580	-0.014	0.895
Letter fluency	0.046	0.676	0.192	0.077	-0.099	0.365	0.072	0.507

Table 72 Correlations of cognitive measure and HDRS-24

6.4 Discussion

Overall no differences were found between the RUL ECT and BT ECT groups for cognitive functioning, except for on the Digit Span Forwards, where a main effect was found between groups. Further tests showed that this difference between groups approached significance at six months follow-up, with RUL participants performing better than BT ECT participants. Overall, all cognitive measures except the MMSE changed significantly over time.

In the RUL group no significant change from baseline was found over time for the Public Events Questionnaire, the Buschke FCSR immediate and delayed recall tasks, Digit Span Backwards, and the TMT-A. A decrease at EOT, with performance returning to baseline levels at follow-up, was found for category and letter fluencies in the RUL ECT group. A significant increase in performance from baseline was found at three or six month follow-up on the ACE-R, the ROCF immediate and delayed recall tasks, the Grooved Pegboard Test and the TMT-B. A significant increase in performance was found in the RUL group at EOT compared to all other time on the Digit Span forwards. The only measure in this group to show a significant decrease over time was the AMI-SF.

In the BT ECT group no significant change over time was found for performance on Digit Span Forwards, Digit Span backwards and TMT-A, although the difference on TMT-A approached significance. A decrease in performance at EOT with a return to baseline levels at follow-up was found for the Public Events Questionnaire, the Buschke FCSR delayed recall task, and category and letter fluency tasks. Significant decreases at EOT with significantly better performance at follow-up compared to baseline were found for the ACE-R and the Buschke FCSR immediate recall tasks. Significant overall increases in performance from baseline were found for the ROCF

immediate and delayed tasks, the Grooved Pegboard and the TMT-B. Again, the only measure with a significant decrease in performance from baseline was the AMI-SF.

6.4.1 Overall differences between RUL and BT ECT

The current investigation has found that the only cognitive function where a significant difference existed between treatment groups was attention, which was significantly better in the RUL ECT group. The general finding of no difference between the rest of the cognitive measures is comparable to a recent study of RUL and BT ECT, in which patients were treated three times each week, where no differences on cognitive measures were found for these treatment types at end of treatment (Kellner et al., 2010a). Performance on Digit Span Forwards was not assessed in the Kellner et al (2010a) study. However this finding is in contrast to other research that has reported performance on cognitive functions to be lower for BT ECT groups than RUL ECT groups (Sackeim et al., 2000, Sackeim et al., 2007). Differences in treatment parameters may be the source of some variations between studies, although treatment frequency is unlikely to account for the difference in the studies mentioned as both the Sackeim (2000 and 2007) and Kellner (2010a) studies administered treatment thrice weekly. The only other measure to approach significance between groups was the AMI-SF, where the RUL ECT group performed better at all follow-up assessments (there were no differences between groups in baseline raw data scores- see page 281, section 6.3). This finding is similar to previous research in which it has been found that BT ECT has more of a detrimental effect on autobiographical memory function than RUL ECT (Sackeim et al., 2000, Sackeim et al., 2007). Performance on some measures was however found to change differently for each treatment across time and this will be discussed next.

6.4.2 Cognitive functioning at End of Treatment

Overall the participants in the BT ECT group had a temporary decrease in performance on the Public Events Questionnaire and verbal learning and memory at EOT that the RUL ECT group did not display. These EOT impairments in the BT ECT group were the only functions that showed worse outcome in the BT ECT group than the RUL ECT group overall. With regard to public events memory function previous studies have also found a decrease in performance at EOT (Calev et al., 1991, Lisanby et al., 2000, Meeter et al., 2011, Sackeim et al., 2000, Sackeim et al., 2008) and this was worse in all studies for BT ECT compared to RUL ECT, thus supporting the findings from the current study.

Similarly, others have reported a worse outcome in BT ECT groups at EOT for verbal learning and memory, compared to RUL ECT (Sackeim et al., 2000, Sackeim et al., 2007, Semkovska and McLoughlin, 2010, Zervas and Jandorf, 1993). However, other studies have reported a significant impairment in verbal learning and memory for participants treated with RUL ECT only (Frasca et al., 2003, Ng et al., 2000). This is in contrast to the current findings where the RUL ECT group did not show significant decrease from baseline in verbal learning and memory at EOT.

RUL ECT had a better temporary effect on attention than BT ECT at EOT, but overall attention did not change from pre-ECT to post-ECT. This finding is similar to a previous study that showed an improvement in attention at EOT in the RUL ECT group only (Sackeim et al., 2007). However others have shown no change in attention after treatment (Porter et al., 2008a) although this was after three treatments only and may have differed at EOT.

6.4.3 Cognitive functioning over three and six month follow-up

Performance on the Public Events Questionnaire and delayed verbal memory returned to baseline levels at follow-up and, along with working memory and psychomotor processing as measured by the TMT-A, did not change overall from baseline to six month follow-up in either group. In relation to previous studies, findings for the Public Events questionnaire are largely in line with what has been reported by others (Lerer et al., 1995, Meeter et al., 2011, Weiner et al., 1986). However one study reported a significant increase in performance at six months (Calev et al., 1991), and although our results have a trend towards better performance at follow-up, this effect was not significant. In contrast to the findings of no change in delayed verbal memory, others have reported an increase in performance from baseline in delayed verbal memory (Ng et al., 2000, Sackeim et al., 2007). Performance on one measure of psychomotor processing was also found to remain unchanged from baseline, which is in line with one previous report (Sackeim et al., 2007), however another measure of psychomotor function improved beyond baseline levels and will be discussed in the next section.

Both BT and RUL ECT had a beneficial effect on the ACE-R, visual learning and memory, psychomotor function as measured by the Grooved Pegboard Test, and executive function as measured by the TMT-B, where performance at follow-up was better than at baseline. Previous studies have also found improved performance at follow-up for executive function and psychomotor speed at short-term follow-up (Semkovska et al., 2010) and for improvements in visual learning and memory (Calev et al., 1991, Sackeim et al., 2007). In addition to this, participants in the BT ECT group had improved performance on verbal learning from baseline. The general improved

performance in verbal learning is similar to previous reports (Ng et al., 2000, Sackeim et al., 2007), however these were not specific to BT ECT.

As stated above the only cognitive function to show a persisting fall in performance from baseline to follow-up was autobiographical memory. This effect was in both groups, although on inspection of average scores this was worse in the RUL ECT group that the BT ECT group. The general finding of persisting autobiographical impairment has also been found in previous research (Lisanby et al., 2000, Sackeim et al., 1993, Sackeim et al., 2007, Sackeim et al., 2008, Squire and Slater, 1983, Squire et al., 1981). In contrast, some reports of improved performance relative to EOT have been published (Calev et al., 1991, Lerer et al., 1995), however the scoring of memory performance was different on measures used in these two tests, in that they allowed for an increase in performance above baseline level, whereas the measure used in the current study did not. As such, the persisting deficit in autobiographical memory may be related, at least in part, to the test itself (AMI-SF). In addition, previous studies have shown healthy controls and depressed controls to also display reduced consistency with baseline at follow-up assessments on the AMI-SF (Lisanby et al., 2000, Weiner et al., 1986), which is in line with previous findings presented in this thesis (section 5.3.1.3.2) and will be discussed further on in section 6.4.5.

Thus, the persistent reduction in consistency of autobiographical memories must be interpreted in terms of the test design and findings in a normal population. Nevertheless, performance in the RUL group was still higher at all times on this measure than performance in the BT ECT group, so the effect of ECT on performance cannot be ruled out. Moreover, the persisting lack of consistency in autobiographical memory needs to be addressed, as perceived changes to autobiographical memory have previously been shown to be of concern to patients who have received ECT (Rose et al.,

2003). As mentioned above the instrument used in this study does not allow for an increase in performance on autobiographical memory at follow-up, and this is likely to have added to the persisting deficits in autobiographical memory seen here. However, the measurement of autobiographical memory will always be difficult, as it is essentially a subjective experience. As such, measures that show consistency with baseline at least provide an objective assessment of how much of what was known remains known at a later time-point. However, it is preferable that controls, or normative data, be used in studies where the AMI-SF is utilised.

6.4.4 Effect of depression severity on cognitive function

Overall the only measure to show a decrease in performance with an increase in depression severity was the Grooved Pegboard Test, and this was at six month follow-up only. As such there is not any reason to suggest that any persisting deficits in autobiographical memory function are depression related. This finding is supported by previous research in which autobiographical memory remained impaired when baseline depression was controlled for (Weiner et al., 1986), but in contrast to one study which showed less severe depression to be related to better performance on the AMI-SF (Sackeim et al., 2007).

6.4.5 Comparison to long-term follow-up in non-ECT depressed and control participants

Although not directly comparable due to study design differences, it is of interest to compare the results of the EFFECT-Dep group presented here with findings from the Mem-Dep study, which examined retrospective memory and cognition in

healthy controls and depressed participants at baseline, six and twelve month follow-up. It must be noted that this is a general, not a statistical, comparison.

With regard to depression severity the three depressed groups (depressed non-ECT participants, RUL ECT participants and BT ECT participants) all scored within two points of each other on the HDRS-24 at baseline. When demographic factors were examined the depressed participants in the Mem-Dep Study were comparable to those in the EFFECT-Dep Trial for gender and scores on the NART. However the EFFECT-Dep group were on average 10 years older than those in the Mem-Dep depressed group, had less third level education in the BT ECT group and, perhaps most strikingly, were much more likely to be treatment resistant, with 57% in the ECT groups meeting criteria compared to 3.5 % in the Mem-Dep Study.

Across the four groups of participants (including healthy controls) the mean scores indicate that healthy controls performed best on all measures at baseline, except for Letter fluency and Buschke FCSR delayed recall, on which depressed non-ECT participants performed marginally better.

With regard to retrograde amnesia in the EFFECT-Dep Trial and retrospective memory function in the MEM-Dep Study, all participants showed similar patterns of performance across time on the AMI-SF and the Public Events Questionnaire. On the Public Events Questionnaire all four groups of participants showed improved performance at follow-up compared to baseline, although this change was significant only in the control and non-ECT depressed participants. Performance at baseline was similar in Mem-Dep Study control and depressed group, but much lower in the two ECT groups.

On the AMI-SF all four groups failed to consistently recall autobiographical memories produced at baseline. However, the control group were most consistent,

followed by the depressed non-ECT group, followed by the RUL ECT group and finally the BT ECT group. Overall the controls were consistent at final follow-up in approximately 80% of memories, the depressed group for approximately 67% of memories, the RUL ECT group for approximately 65% of memories and the BT ECT group for approximately 59% of memories.

Performance on the Digit Span Forwards, Trail Making Test A, category and letter fluency, delayed verbal memory and the MMSE showed no significant change across time for all groups, although the ECT groups scored considerably worse than either the depressed or control groups in the Mem-Dep study at baseline, except for performance on the MMSE and Digit Span forward which were comparable across all groups. Performance on the visual learning and memory tasks showed a significant and similar improvement in performance across time for all four groups, again with the ECT groups performing less well than either the depressed of healthy control group.

Participants in the Mem-Dep Study and the EFFECT-Dep Trial showed different patterns of performance on four variables only- the Grooved Pegboard Test, the Trail Making Test B, verbal learning on the Buschke FCSR and performance on the ACE-R. On these measures the participants in the Mem-Dep Study did not show change across time, but participants in the ECT groups showed significant improvement at follow-up compared to baseline. Again, the ECT groups had much poorer performance on these measures to begin with and did not reach the same level as depressed non-ECT or control participants at follow-up, despite the improvements made.

The other notable difference between non-ECT depressed participants and ECT groups was that performance was not significantly worse on any measure (except the AMI-SF) at any time in the Mem-Dep Study, whereas performance was significantly worse at EOT in the BT ECT group on the Public Events Questionnaire and verbal

learning and memory. This was clearly a transient effect of the treatment received (BT ECT), as mentioned above.

6.4.6 Conclusions

These preliminary results of cognitive functioning from the EFFECT-Dep Trial have shown no differences between high-dose RUL ECT and standard dose BT ECT for any cognitive measure other than attention, for which RUL ECT had a more favourable outcome than BT ECT. In terms of general cognition (not including retrograde memory), performance was not impaired on any measure in the RUL ECT group over time, whereas verbal learning and memory were lower than pre-ECT levels in the BT ECT group. In terms of retrograde memory, there was dissociation between the effects of ECT type on public events memory function, with BT ECT participants showing worse performance at EOT. Finally, although autobiographical memory performance was more affected by BT ECT than RUL ECT, this finding was not significant. Overall, the hypothesis that autobiographical memory would be more affected by ECT than public events memory is supported; however the hypothesis that RUL ECT would have a lesser effect on cognition than BT ECT is only partially supported by these findings.

It is important to note that only performance of autobiographical memory function remained lower than baseline at six months follow-up. Thus, cognitive functioning in general was either unaffected or improved after ECT. This finding adds to the growing body of evidence that shows that negative cognitive effects of ECT are transient.

The general comparison with findings from the Mem-Dep study suggests that performance of participants in the ECT groups was considerably lower to begin with, despite having the same severity of depression. This suggests that some other factor,

such as increased age, lower education, treatment resistance, or possibly previous ECT contribute to the lowered cognitive functioning apparent in the ECT groups. In the current study those with previous ECT performed at a significantly lower level than those who had never received ECT on tasks of general cognitive functioning (MMSE) and psychomotor speed, but not on autobiographical memory or any other variable.

6.4.7 Strengths, limitations and future directions

The findings reported here are preliminary findings of The EFFECT-Dep Trial, which examines efficacy and cognitive effects of high-dose RUL and standard-dose BT ECT. Although not based on the complete dataset, this study has numerous strengths. In particular, these findings are part of a randomised controlled trial (RCT), which is the current gold-standard in clinical research practice.

Secondly, this study addresses both retrograde and anterograde memory functions, as well as general cognitive function, and as such provides a broad picture of the effects of ECT on cognitive functioning. Moreover, two forms of retrograde memory function have been assessed here, allowing for examination of differential effects of ECT on these functions which are often reported to be impaired after ECT treatment. Finally, participants in this study were assessed both at end of treatment and at longer term follow-up points, which allowed for investigation of acute changes and recovery of function in the same population.

As the EFFECT-Dep trial is on-going the efficacy of each treatment type could not be assessed, and as such an overall impression of the effect of change in depression severity on cognitive function could not be examined. However, this limitation was addressed by correlating combined HDRS-24 scores from the RUL and BT ECT groups with cognitive measures at each time-point, to get a sense of the relationship between depression severity and cognitive function.

A second limitation here, is the absence of controls in this study. As mentioned above RCT's are the current gold-standard in clinical research, as the random allocation of participants to different treatments reduces the possibility that groups were different to begin with, and increases the chances that any differences found are in fact due to the treatment condition and not to other variables. The only way to include controls in an RCT study such as this one would be to randomise participants to either sham-ECT or a waiting list group. Neither of these situations is ethically acceptable, given the fact that patients referred for ECT are usually severely depressed and often in need of urgent treatment (National Institute for Clinical Excellence, 2009). As such, one option is for researchers to carry out assessments using the same measures, at the same time-points, in a healthy control population. Although this additional data could not be directly compared to the RCT groups, as they would not have been randomised to any condition, it would still be useful in that it would allow for interpretation of findings in the ECT group in light of these norms.

Another limitation, as previously mentioned, it the difficulty in measuring autobiographical memory function. The AMI-SF is currently the most commonly used measure of autobiographical memory consistency in ECT studies (Kellner et al., 2010a, McCall et al., 2000, McElhiney et al., 1995, Sackeim et al., 1993, Sackeim et al., 2000, Sackeim et al., 2007, Weiner et al., 1986) and is useful in providing a measure of consistency of recall. However, in only measuring consistency it does not allow for improvements in autobiographical memory function to be assessed, if they occur. To address this issue a future study could use the AMI-SF and another instrument that allows for improvements in performance to be measured, in two groups of ECT participants. In this way it could first be investigated whether ECT patients can provide extra details at follow-up. When this is ascertained a new measure could be devised,

combining existing tests of both consistency of recall, and amount of details that can be provided. For example, details for the same events can still be assessed at each time-point (as in the AMI-SF), but extra details, and additional memories provided in addition to those provided at baseline could also be scored. As such a new measure could provide scores for both consistency with original details and overall amount of details provided at each assessment. In this way any improvements in autobiographical memory could be recorded. A drawback of this method would be the extra time it would take to administer and score the new autobiographical memory measure, which would need to be taken into account when working with severely depressed patients. However, the analyses of such an instrument would provide important information about changes to autobiographical memory performance over time and over the course of a depressive episode. Normative data from a large sample should be collected for any future measures of autobiographical memory so that any findings can be interpreted in light of normal changes in autobiographical memory over time. The final chapter will discuss the findings from healthy controls, non-ECT treated depressed participants and ECT treated patients with respect to overall patterns and important findings.

CHAPTER 7: OVERALL CONCLUSIONS

7.1 Overall aims and objectives

Cognitive impairments in anterograde memory, attention, psychomotor processing and executive function have been found to accompany major depressive episodes (Austin et al., 2001). In recent years interest has grown in determining whether the lowered cognitive performance seen in depression is linked to depression severity (state) or an underlying cognitive impairment in those who suffer from depression (trait). As such, some researchers have sought to examine cognitive functioning both during a depressive episode and over follow-up periods of up to two years (Biringer et al., 2007, Douglas and Porter, 2009, Gallassi et al., 2006). However, retrospective memory function is rarely studied with respect to changes in function both during and after a depressive episode. This is especially surprising given the importance of studying retrograde amnesia after electroconvulsive therapy (ECT) for depression, as it is one of the cognitive functions that is most often found to be affected after ECT (Sackeim et al., 2007, Sackeim et al., 1993, Sackeim et al., 2000, Sackeim et al., 2008, McCall et al., 2000, Lerer et al., 1995, Calev et al., 1991, Lisanby et al., 2000, Squire et al., 1981) and retrospective memory deficits are reported as a serious concern for ECT patients (Rose et al., 2003). Thus it is important to attempt to untangle the effects of depression and ECT on retrospective memory, both during the depressive episode and over follow-up.

In addition, study of depressed and ECT patients over time will add to information regarding the change in cognitive functioning over the course of a depressive episode. Two facets of retrospective memory were examined here: autobiographical memory and public events memory function. In order to study public

events memory function a new measure (based on previous studies (Reed and Squire, 1998, Squire et al., 1989, Warrington and Silberstein, 1970)) was devised and examined for reliability.

The main objectives of this work therefore were to examine effects of depression on retrospective memory in depressed patients receiving pharmacotherapy treatment, in comparison to healthy controls, and to examine retrograde memory function in patients participating in a randomised controlled non-inferiority trial investigating the effectiveness and side-effects of high-dose RUL ECT and standard BL ECT in severe depression. This was achieved by examining patients and controls from two separate parallel studies. The first was The Mem-Dep Study, a study of retrospective memory and general cognition in unipolar depression and healthy controls, during a depressive episode and up to one year follow-up. The second study involved preliminary findings from the EFFECT-Dep Randomised Controlled Trial, which focused on enhancing the effectiveness, and investigating cognitive side-effects of electroconvulsive therapy in severe depression, by comparing standard dose bitemporal ECT (BT ECT) with high-dose right unilateral ECT (RUL ECT). In the current study cognitive outcomes were examined at baseline and up to six months post-treatment.

7.2 Overall findings

The first results chapter examined the reliability of the construction and updating of a Public Events Questionnaire. Analyses relating to internal consistency, parallel version reliability and item difficulty suggested that the Public Events Questionnaire was reliable when constructed in a standardised manner. In addition, the test-retest reliability of the questionnaire was good across all versions of the

questionnaire studied. Therefore the questionnaire provides a reliable measure of the consistency of public events memory over time. The method described is suitable for constructing and updating future questionnaires which can be tailored for use with any particular population and updated periodically with ease.

Findings from Chapter 4, relating to differences in cognitive function between healthy controls and depressed participants during the acute phase of a depressive episode, indicated that autobiographical memory and psychomotor speed and processing may be most affected during the acute phase of a depressive episode. Executive function may also be affected, but it is unclear whether this is associated directly with depression or with background demographic factors such as education, age and gender. Overall, individuals in the acute depressive phase appeared to have generally lowered performance across the range of cognitive domains studied, including retrospective memory, anterograde verbal and visual learning and memory, attention, psychomotor processing and executive function. Persisting lowered performance was found in autobiographical memory and psychomotor speed and processing after treatment. Performance on tasks of immediate and delayed visual memory, as well as psychomotor function (Trail Making Test A) was found to be associated with severity of depression, where more severe depression was linked with poorer performance. However, a clear state or trait relationship was difficult to ascertain as the depressed group, on average, remained moderately depressed at the two month follow-up.

Over the one year follow-up in the Mem-Dep Study, autobiographical and public events retrospective memory functions were found to be differentially affected in depression. Autobiographical memory performance decreased over time in both depressed and control participants, whereas public events memory function increased, again in both depressed and control participants. Autobiographical memory of

depressed participants was also more affected at baseline and less consistent over time than performance in the control group. In addition, findings suggested that depression may lead to mild impairments in attention, psychomotor speed and processing, and some aspects of executive function, compared to controls, but the evidence for this in the present study is not conclusive. This is possibly due to the small number of participants in some analyses, thus limiting the power to detect differences between groups.

The preliminary findings from the investigation of cognitive functioning from the EFFECT-Dep Trial found no differences between high-dose RUL ECT and standard dose BT ECT for any cognitive measure other than attention, for which RUL ECT had a more favourable outcome than BT ECT. In terms of general cognition RUL ECT did not have any adverse effect on cognitive function with regards to anterograde memory, attention, psychomotor processing and executive functioning. However, verbal learning and memory were adversely affected at end of treatment in the BT ECT group. Despite this, all general cognitive functions returned to baseline level performance, or better, at six months follow-up. In terms of retrograde amnesia, there was a dissociation between the effects of ECT type on public events memory function, with BT ECT participants showing worse performance post treatment. Although autobiographical memory performance was more affected by BT ECT than RUL ECT, this finding was not significant. Importantly, only performance of autobiographical memory function remained lower than baseline at six months follow-up. Thus, cognitive functioning in general was either unaffected or improved after ECT. This finding adds to the growing body of evidence that shows that negative cognitive effects of ECT are transient.

The general comparison with findings from the Mem-Dep study suggests that performance of participants in the ECT groups was considerably lower to begin with,

despite all depressed participants across studies having the same level of depression severity at baseline. This indicates that some other factor besides depression, or importantly, the ECT itself, contributed to the lowered cognitive functioning which is apparent in the ECT groups compared to the non-ECT depressed group. The ECT group was found to have less third level education, higher age and more than 50% more participants who were classed as treatment resistant, and thus these factors need to be investigated more thoroughly with regard to outcome after ECT.

7.3 Reflections on this thesis

On commencing the research outlined in this thesis I hoped to learn much about depression, electroconvulsive therapy and their effects on cognition. I feel I have accomplished this goal, however I feel that I have learned much more about the wider goals and practice of research along the way. One of the difficulties I faced at the beginning of this study was how to work well as part of a large, multidisciplinary team, learning what I could from others, but also learning how to develop my own research strengths and find my specific place within that team. To do this I had to learn how to balance my duties towards the team while developing confidence and competency in my own research. Another important experience has been working within a busy clinical setting, with a clinical population. While research ideas are often developed and begun in a laboratory or academic setting, they must also work in the environment they are to be applied to. In this case the recruitment and assessment of participants was mainly undertaken in a busy psychiatric hospital in Dublin. Any research activities had to fit around the clinical care of the patients, whose main reason for being there was to receive treatment for depression. Due to the nature of depressive illness and the

difficulties it involves for the patient, such as tiredness, rumination, worthlessness and difficulty with concentration, recruitment and assessment of participants for the studies outlined here often proceeded at a slower pace than originally envisioned. In addition, it is now clear to me that patients hospitalised for treatment for a major depressive episode are rarely suffering with a clear-cut diagnosis of unipolar depression, and more often than not have at least one comorbid diagnosis. Thus, now armed with substantially more experience than when I began this course of study, it's easier to see how the research could have proceeded differently. For example, although I felt it important to have a pure unipolar depressed sample in the Mem-Dep study, with no comorbidities, obtaining this sample proved extremely difficult and time consuming. One response to this might have been to widen the study criteria to include anxiety disorders, and accounting for any of their effects during analysis of responses. Another alternative might have been to recruit participants from multiple sites, however this would have been much more time consuming and required either more researchers or less involvement in the EFFECT-Dep study. Another perhaps ambitious element of the current studies was in using such a wide ranging assessment battery and following up participants over a 12 month period. The drop-out rate would suggest that one or both of these elements was not suitable for the specific samples used in these studies. In may have been more successful to use a more specific, shorter, assessment battery or else to follow-up over a shorter time-period, for example six months. However, I feel that the 12 month follow-up was important in the Mem-Dep study, so perhaps a narrower range of assessments would have been the better choice here. Overall, I feel that due to undertaking this research thesis I have learned much more than I originally expected about the wider practice of real-world, large-scale research, and that practical

knowledge gained from real experience should always be considered alongside peer-reviewed publications.

7.4 Conclusions

This research has highlighted a number of important findings, the most notable of which include the following: the importance of studying the consistency of retrospective memory in non-ECT treated patients and healthy controls in order to reliably interpret the findings with other groups, such as ECT patients; the importance of assessing healthy controls at the same time-points as clinical participants in longitudinal research; the differential acute and long-term effects of different ECT treatment parameters on cognitive function; and the importance of examining background demographic and clinical histories of participants to obtain a cohesive understanding of the various processes that can affect cognitive functioning during a depressive episode and treatment with ECT. Taken together these findings might be used to inform prospective ECT patients about the long-term effects of ECT upon cognition, that is, that based upon both studies ECT is unlikely to have an effect on public events memory but may have some effect on Autobiographical memories. However, these findings are preliminary and subject to change, therefore at this point it would not be prudent to use this information prematurely. Following on from this, these findings suggest that routine monitoring of cognitive function before, during and after a course of ECT should include some measure of autobiographical memory. However, due to the difficulties inherent in assessment of autobiographical memory as discussed earlier (section 1.3.1.3.2) this is likely to prove challenging. A shorter version of an autobiographical memory test, for example addressing 50% of memories provided at

baseline, may be one possibility in this situation; however more research will need to be undertaken around this important consideration in order to devise a beneficial yet practical assessment.

The findings of the current research are important in aiding the understanding of the ways in which time, treatments and depression itself effect cognition, and in particular retrospective memory functioning. It is anticipated that three papers will be submitted for publication based on the findings of the public events reliability study and the Mem-Dep study, specifically: one paper detailing the methods of developing and updating a public events questionnaire and reliability data obtained regarding the same; one paper on the longitudinal findings of cognitive functioning in depression; and a final paper outlining the specific changes to retrospective memory over 12 month follow-up in depressed participants and healthy controls. Papers regarding the effects of ECT type on efficacy and side-effect profile will be published with other researchers involved at the conclusion of the EFFECT-Dep RCT.

Future follow-up work arising from the research finding reported in this thesis could focus on the development of a new instrument for assessing both consistency and specificity of autobiographical memory in clinical populations. Furthermore, as noted above, variables relating to previous occasions and types of treatments received should be investigated thoroughly to tease out their effects on cognitive functioning before, during and after ECT.

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APPENDIX 1: BACKGROUND INFORMATION SHEET

EFFECT-*Dep Study Patient Information*

Please Circle or Fill as Appropriate

Surname: _____

First Name: _____

Insert Patient Label Here

Date of Birth: ___/___/_____

Age: _____

Date Filed___/___/___

_____

_____

Educational Attainment:

Primary Secondary Tertiary

Quaternary

Marital Status:

Married ☐
Unmarried ☐
Divorced ☐
Widowed ☐

Socioeconomic Group_____

1	Professional
2	Managerial & Technical
3N	Skilled Occupations – Non-Manual
3M	Skilled Occupations - Manual
4	Partly skilled
5	Unskilled Occupations

Address:

_____
_____
_____
_____
_____
_____
_____
_____

_____

Phone:_____

Mobile:_____

Weight (kg):_____
1kg = 2.205 lbs, 1 stone = 14lbs

Height (m):_____

Next of Kin :

Name _____

Relation to Patient:_____

Contact Details:

_Phone:_____
_Mobile:_____
_email:_____

Address:

_____
_____
_____
_____
_____
_____

Occupation:_____

_____
_____
_____

Previous ECT: YES / NO

Date of Last ECT : ____/____/____

Source of Referral: St.JH / St.EH / St.PH

Smoker Y / N

Alcohol : Regular Alcohol Intake: _____U/wk

Family History of Mental Illness:

Relation to patient	Nature of illness

APPENDIX 2:STRUCTURED CLINICAL INTERVIEW FOR DSM-IV (SCID-I)

SCID-I (DSM-IV) Version 2.0 Current MDE (FEB 1996 FINAL) Mood Episodes A.1

A. MOOD EPISODES

IN THIS SECTION, MAJOR DEPRESSIVE, MANIC, HYPOMANIC EPSIODES, DYSTHYMIC DISORDER, MOOD DISORDER DUE TO A GENERAL MEDICAL CONDITION, SUBSTANCE-INDUCED MOOD DISORDER, AND EPSIODE SPECIFIERS ARE EVALUATED.

	CURRENT MAJOR DEPRESSIVE EPISODE	**MDE CRITERIA**				
		A. Five (or more) of the following symptoms have been present during the same two-week period and represent a change from previous functioning; **at least one** of the symptoms is either **(1) depressed mood, or (2) loss of interest or pleasure.**				
(1)	In the last month . . . . . . has there been a period of time when you were feeling depressed or down most of the day nearly every day? (What was that like?) If YES: How long did it last? (As long as two weeks?)	1) **depressed mood** most of the day, nearly every day, as indicated either by subjective report (e.g. feels sad or empty) or observation made by others (e.g. appears tearful)	?	1	2	3
(2)	+ . . . what about losing interest or pleasure in things you usually enjoyed? IF YES: Was it nearly every day? How long did it last? (As long as two weeks?)	(2) markedly **diminished interest or pleasure** in all, or almost all, activities most of the day, nearly every day (as indicated either by subjective account or observation made by others).	?	1	2	3

NOTE: WHEN RATING THE FOLLOWING ITEMS, CODE "1" IF CLEARLY DUE TO A GENERAL MEDICAL CONDITION, OR TO MOOD-INCONGRUENT DELUSIONS OR HALLUCINATIONS

? = inadequate information 1= absent or false 2=subthreshold 3=threshold or true

	FOR THE FOLLOWING QUESTIONS, FOCUS ON THE WORST TWO WEEKS IN THE PAST MONTH (OR ELSE THE PAST TWO WEEKS IF EQUALLY DEPRESSED FOR ENTIRE MONTH) During this (TWO WEEK PERIOD)					
(3)	. . did you lose or gain any weight? (How much?) (Were you trying to lose weight?) IF NO: How was your appetite? (What about compared to your usual appetite?) (Did you have to force yourself to eat?) (Eat [less/more] than usual? (Was that nearly every day?)	(3) **significant weight loss** when not dieting, or weight gain (e.g. a change of more than 5% of body weight in a month) or decrease or increase in appetite nearly every day. Check if: ____ weight loss or decreased appetite ____ weight gain or increased appetite	?	1	2	3	
(4)	. . how were you sleeping? (Trouble falling asleep, waking frequently, trouble staying asleep, waking too early, OR sleeping too much? How many hours a night compared to usual? Was that nearly every night?)	(4) **insomnia or hypersomnia** nearly every day Check if: _____ insomnia _____ hypersomnia	?	1	2	3	
(5)	. . were you so fidgety or restless that you were unable to sit still? (Was it so bad that other people noticed it? What did they notice? Was that nearly every day?) IF NO: What about the opposite – talking or moving more slowly than is normal for you? (Was it so bad that other people noticed it? What did they notice? Was that nearly every day?)	(5) **psychomotor agitation or retardation** nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down) NOTE: CONSIDER BEHAVIOUR DURING THE INTERVIEW Check if: _____ psychomotor retardation _____ psychomotor agitation	?	1	2	3	
(6)	. . what was your energy like? (Tired all the time? Nearly every day?)	(6) **fatigue or loss of energy nearly every day**	?	1	2	3	

? = inadequate information 1= absent or false 2=subthreshold 3=threshold or true

(7)	During this time . . how did you feel about yourself? (Worthless?) (Nearly every day?) IF NO: What about feeling guilty about things you had done or not done? (Nearly every day?)	(7) **feelings of worthlessness or excessive or inappropriate guilt** (which may be delusional) nearly every day (not merely self-reproach or guild about being sick) NOTE: CODE "1" or "2" IF ONLY LOW SELF-ESTEEM Check if: _____ worthlessness _____ inappropriate guilt	?	1	2	3	
(8)	. . did you have trouble thinking or concentrating? (What kinds of things did it interfere with?) (Nearly every day?) IF NO: Was it hard to make decisions about everyday things? (Nearly every day?)	(8) **diminished ability to think or concentrate,** or indecisiveness, nearly every day (either by subjective account or as observed by others) Check if: _____diminshed ability to think _____ indecisiveness	?	1	2	3	
(9)	. . were things so bad that you were thinking a lot about death or that you would be better off dead? What about thinking of hurting yourself? IF YES: Did you do anything to hurt yourself?	(9) **recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation** without a specific plan, or a suicide attempt or a specific plan for committing suicide NOTE: CODE "1" FOR SELF-MUTILATION W/O SUICIDAL INTENT Check if: _____ thoughts of own death _____ suicidal ideation _____ specific plan _____ suicide attempt	?	1	2	3	
		AT LEAST FIVE OF THE ABOVE SXS [A (1-9)] ARE CODED "3" AND AT LEAST ONE OF THESE IS ITEM (1) OR (2) NOTE: DSM-IV criterion B (i.e. does not meet criteria for a Mixed Episode) has been omitted from the SCID		1		3	

? = inadequate information 1= absent or false 2=subthreshold 3=threshold or true

Have any of the above symptoms Interfered with your day to day Activities?	C. The symptoms cause **clinically Significant distress or impairment in social, occupational or other important areas of functioning.**	1 3	
Did this begin soon after someone close to you died?	D. Not better accounted for by **bereavement,** i.e., after the loss of a loved one, the symptoms persist for longer than 2 months or are characterized by marked functional impairment, morbid preoccupation with worthlessness, suicidal ideation, psychotic symptoms, or psychomotor retardation.	1 3 SIMPLE BEREAVE-MENT NOT SIMPLE BEREAVE-MENT	
	MAJOR DEPRESSIVE EPISODE CRITERIA A, C AND D ARE CODED "3"	1 3	
How many separate times in your life have you been (depressed/ OWN WORDS) nearly every day for at least two weeks and had several of the symptoms that you described, like (SXS OF WORST EPISODE)?	**Total number of Major Depressive Episodes, including current** (CODE 99 IF TOO NUMEROUS OR INDISTINCT TO COUNT)		

? = inadequate information 1= absent or false 2=subthreshold 3=threshold or true

CURRENT MAJOR DEPRESSIVE EPISODE SPECIFIERS

WITH POSTPARTUM ONSET	**WITH POSTPARTUM ONSET**					
IF UNKNOWN: When did (DEPRESSIVE SXS) start?	Onset of episode within 4 weeks postpartum	?	1		3 WITH POST-PARTUM ONSET	
WITH CATATONIC FEATURES	**CATATONIC FEATURES CRITERIA**					
BY OBSERVATION OR HISTORY	The clinical picture is dominated by **at least 2** of the following:					
	(1) **motoric immobility** as evidenced by catalepsy (including waxy flexibility) or stupor DESCRIBE SPECIFIC BEHAVIOR:	?	1	2	3	
	(2) **excessive motor activity** (that is apparently purposeless and not influenced by external stimuli) DESCRIBE SPECIFIC BEHAVIOR:	?	1	2	3	
	(3) **extreme negativisim** (an apparently motiveless resistance to all instructions or maintenance of a rigid posture against attempts to be moved) or mutism DESCRIBE SPECIFIC BEHAVIOR:	?	1	2	3	
	(4) **peculiarities of voluntary movement** as evidenced by posturing (voluntary assumption of inappropriate or bizarre postures), stereotyped movements, prominent mannerisms, or prominent grimacing DESCRIBE SPECIFIC BEHAVIOR:	?	1	2	3	

? = inadequate information 1= absent or false 2=subthreshold 3=threshold or true

	(5) **echolalia** (the pathological parrotlike and apparently senseless repetition of a word or phrase just spoken by another person) or echopraxia (the repetitive imitation of the movements of another person) DESCRIBE SPECIFIC BEHAVIOR:	? 1 2 3	
	AT LEAST 2 ITEMS ARE CODED "3"	1 3 GO TO ***MEL-ANCHOLIC FEATURES*** **WITH CATA-TONIC FEAT-URES**	

? = inadequate information 1= absent or false 2=subthreshold 3=threshold or true

APPENDIX 3 TREATMENT REVIEW

Mem-Dep Study Treatment Review

Please circle or fill out as appropriate

Assessor initials _____ Date ___/____/___

Trial number _____

Age _____ Date of Birth ___/___/___

Baseline Medications:

Medication Name	Dose	Times / day	Time since started on this treatment	Compliant? (Yes/ No)

2 month follow-up medications:

Medication Name	Dose	Times / day	Time since started on this treatment	Compliant? (Yes/ No)

6 month follow-up medications:

Medication Name	Dose	Times / day	Time since started on this treatment	Compliant? (Yes/ No)

12 month follow-up medications:

Medication Name	Dose	Times / day	Time since started on this treatment	Compliant? (Yes/ No)

APPENDIX 4: THE ANTI-DEPRESSANT TREATMENT HISTORY FORM (ATHF)

OPT ECT

ANTIDEPRESSANT TREATMENT HISTORY FORM (ATHF) CURRENT EPISODE

SITE INITIALS	SUBJECT NUMBER	SUBJECT INITIALS	DATE OF ONSET

FROM SCID:			
	Date of Onset of Episode (mo/yr)		☐ 1 Unipolar Psychotic ☐ 2 Unipolar Nonpsychotic ☐ 3 Bipolar Psychotic ☐ 4 Bipolar Nonpsychotic
	Length of Episode (wks)		

Source of Information	Reliability of source	Outcome
1 Interview	1 Excellent	-1 Worse
2 Patient Record	2 Good	0 No Change
3 Pharmacy	3 Adequate	1 Marginally Improved
4 Family Member	4 Poor	2 Markedly Improved
5 Prescribing physician		3 Remitted
6 Therapist		9 No Information

ECT DEVICE		DOSE	DURATION			REASON STOPPED	OUTCOME
uni/bilateral	% related to threshold	(mC, J, V)	Start date	Stop date	Total No.		

Form #
Page 1

ANTIDEPRESSANT TREATMENT HISTORY FORM (ATHF) CURRENT EPISODE

MEDICATION		DOSE	DURATION			REASON STOPPED	OUTCOME
Generic Name	Blood Level	mg/day	Start date	Stop date	Total (wks)		

Form #
Page 2

ANTIDEPRESSANT TREATMENT HISTORY FORM (ATHF) CURRENT EPISODE

MEDICATION		DOSE	DURATION			REASON STOPPED	OUTCOME
Generic Name	Blood Level	mg/day	Start date	Stop date	Total (wks)		

Form #
Page 3

ANTIDEPRESSANT TREATMENT HISTORY FORM (ATHF) CURRENT EPISODE

Treatment Trial (Period Rated) Dates		Antidepressant Type	Combination/ Antidepressant Trial	Specific Rating	Specific Rating	Specific Rating	Specific Rating	Specific Ratir
Start	Stop	Specify Generic Name(s) or ECT	Yes or No	See Criteria	See Anchors	Dose	Duration/ # of ECT	Compliance	Outcome

Form #
Page 4

ATHF Instructions: Rating Medication Trials for Antidepressant Potency

TCA/Tetracyclic

I. Amitriptyline(Elavil, Endep), imipramine(Tofranil), desipramine(Norpramine, Pertofrane), trimipramine(Surmontil), clomipramine (Anafranil), maprotilene(Ludiomil), doxepin(Sinequan,

Adapin), nomifensine.

By dosage:

1 any drug < 4 wks OR any drug < 100 mg/d

2 4 wks or more and 100-199 mg/d

3 4 wks or more and 200-299 mg/d

4 4 wks or more and ≥ 300 mg/d

By blood level: imipramine and desimipramine only; levels take precedence

4 4 wks or more and DMI level ≥ 125 ng/ml

4 4 wks or more and IMI + DMI ≥ 225 ng/ml

II. Nortriptyline(Pamelor, Aventyl)

By blood level: levels take precedence

1 NT < 4 wks

2 4 wks or more and level < 50 ng/ml

3 4 wks or more and level 50-99 ng/ml

4 4 wks or more and level 100-150 ng/ml

By dosage:

1 NT < 4 wks OR

4 wks or more and NT < 50 mg/d

2 4 wks or more and NT 50-75 mg/d

3 4 wks or more and NT 76-100 mg/d

4 4 wks or more and NT > 100

III. Protriptyline(Vivactil)

1 drug < 4 wks OR 4 wks or more and dosage ≤ 30 mg/d

2 4 wks or more and dosage 31-40 mg/d

3 4 wks or more and dosage 41-60 mg/d

4 4 wks or more and dosage > 60 mg/d

NOTES:
For TCA-MAOI combinations: score each agent alone, as a separate trial
For TCA-paroxetine/fluoxetine combination trials: after one week on 20 mg of paroxetine or fluoxetine the dosage equivalent of the TCA should be doubled to determine resistance rating

SSRIs

I. Fluoxetine(Prozac), citalopram (Celexa)

1 drug < 4 wks OR 4 wks or more and dosage 1-9 mg/d
2 4 wks or more and dosage 10-19 mg/d
3 4 wks or more and dosage 20-39 mg/d
4 4 wks or more and dosage ≥ 40 mg/d

II. Fluvoxamine(Luvox)

1 drug < 4 wks OR drug < 100 mg/d
2 4 wks or more and 100-199 mg/d
3 4 wks or more and 200-299 mg/d
4 4 wks or more and ≥ 300 mg/d

III. Paroxetine(Paxil)

1 less than 4 wks OR
4 wks or more and dosage 1-9 mg/d
2 4 wks or more and dosage 10-19 mg/d
3 4 wks or more and dosage 20-29 mg/d
4 4 wks or more and dosage ≥ 30 mg/d

IV. Sertraline(Zoloft):

1 drug < 4 wks OR
4 wks or more and dosage < 50 mg/d
2 4 wks or more and dosage 50-99 mg/d
3 4 wks or more and dosage 100-199 mg/d
4 4 wks or more and dosage ! 200 mg/d

Other Antidepressants

I. Bupropion(Wellbutrin)

1 drug < 4 wks OR 4 wks or more and dosage < 150 mg/d
2 4 wks or more and dosage 150-299 mg/d
3 4 wks or more and dosage 300-449 mg/d
4 4 wks or more and dosage ≥ 450 mg/d

II. Mirtazapine(Remeron)

1 less than 4 wks OR
4 wks or more and dosage < 15 mg/d
2 4 wks or more and dosage 15-29 mg/d
3 4 wks or more and dosage 30-44 mg/d
4 4 wks or more and dosage ≥ 45 mg/d

III. Nefazodone(Serzone)

1 drug < 4 wks OR 4 wks or more and dosage < 150 mg/d
2 4 wks or more and dosage 150-299 mg/d
3 4 wks or more and dosage 300-599 mg/d
4 4 wks or more and dosage ≥ 600 mg/d

IV. Trazodone(Desyrel), amoxapine(Ascendin)*

1 drug < 4 wks OR 4 wks or more and dosage < 200 mg/d
2 4 wks or more and dosage 200-399 mg/d
3 4 wks or more and dosage 400-599 mg/d
4 4 wks or more and dosage ≥ 600 mg/d

*Amoxapine will also receive an antipsychotic rating

V. Venlafaxine(Effexor and Effexor XR)

1 less than 4 wks OR
4 wks or more and dosage < 75 mg/d
2 4 wks or more and dosage 75-224 mg/d
3 4 wks or more and dosage 225-374 mg/d
4 4 wks or more and dosage ≥ 375 mg/d

MAOIs

I. Phenelzine(Nardil)

1 drug < 4 wks OR 4 wks or more and dosage ≤ 30 mg/d
2 4 wks or more and dosage 31-60 mg/d
3 4 wks or more and dosage 61-90 mg/d
4 4 wks or more and dosage 91 mg/d or greater

II. Moclobemide

1 less than 4 wks OR 4 wks or more and dosage < 150 mg/d
2 4 wks or more and dosage 150-299 mg/d (100-200=30 Nardil)
3 4 wks or more and dosage 300-599 mg/d (300=60 Nardil)
4 4 wks or more and dosage ≥ 600 mg/d (600 = 90 Nardil)

III. Selegiline(Eldepryl)

1 drug < 4 wks OR 4 wks or more and dosage ≤ 20 mg/d
2 4 wks or more and dosage 21 - 40 mg/d
3 4 wks or more and dosage 41 - 59 mg/d
4 4 wks or more and dosage ≥ 60 mg/d

IV. Tranylcypromine(Parnate), isocarboxazid(Marplan)

1 drug < 4 wks OR 4 wks or more and dosage ≤ 20 mg/d
2 4 wks or more and dosage 21-40 mg/d
3 4 wks or more and dosage 41-60 mg/d
4 4 wks or more and dosage ≥ 61 mg/d

NOTES:
MAOI inhibition: 80% inhibition will rate 4
For TCA-MAOI combinations, score each agent considered alone
TCA/SSRI and any other combinations, e.g. SSRI/bupropion, should be treated as TCA/MAOI combinations: rate each medication separately

Lithium

I. Lithium alone

For bipolar patients: levels take precedence over dosage

1 drug < 4 wks OR 4 wks or more and level: ≤ 0.4 mEq/L OR
4 wks or more and dosage: < 600 mg/d for any duration
2 4 wks or more and level: 0.41-0.6 mEq/L OR
4 wks or more and dosage: 600- 899 mg/d
3 4 wks or more and level: > 0.6 mEq/L OR
4 wks or more and dosage: ≥ 900 mg/d

Unipolar patients can receive a maximum rating of 2 for Li alone

II. Lithium as an augmenting agent

4 antidepressant drugs I - IX rated level 3 and Li for at least 2 wks CBZ rated level 3 and Li for at least 2 wks
5 antidepressant drugs I - IX rated level 4 and Li for at least 2 wks

Benzodiazepines

I. Alprazolam(Xanax)

1 alprazolam < 4 wks OR 4 wks or more and dosage < 4 mg/d
2 4 wks or more and dosage 4 mg/d or greater

II. Other benzodiazepines

1 any dosage for any duration
These drugs are not considered augmenting agents.

Anticonvulsants

I. Carbamazepine(Tegretol)

For bipolar patients:

1 CBZ < 4 wks OR 4 wks or more and level < 6

2 4 wks or more and level 6 - 7.9

3 4 wks or more and level ≥ 8

Unipolar patients can receive a maximum rating of 2 for CBZ alone

II. Lamotrigine (Lamictal)

For bipolar patients:

1 drug < 4 wks OR 4 wks or more and dosage < 50 mg/d

2 4 wks or more and dosage 50-199 mg/d

3 4 wks or more and dosage ≥ 200 mg/d

Unipolar patients can receive a maximum rating of 2 for Lamotrigine alone

III. Gabapentin (Neurontin)

For bipolar patients

1 drug < 4 wks OR 4 wks or more and dosage ≤ 800 mg/d

2 4 wks or more and dosage ≥ 1,600 mg/d

Unipolar patients can receive a maximum score of 1 for Gabapentin alone

IV. Clonazepam(Klonopin), valproic acid(Depakene) , and topiramate (Topamax) can be rated 1 if used alone; they are not considered augmenting agents

APPENDIX 5: HAMILTON DEPRESSION RATING SCALE 24 ITEM

Patient's Name _____

Patient's Number _____

Date _____

Assessment no. _____

HRSD 24 (Modified from Williams SIGH-D 1998) with 3 items taken from W. Guy - ECDEU Manual for assessment in psychopharmacology NIMH 1976

1. Depressed Mood

What's your mood been like this past week?

Have you been feeling down or depressed?

Sad? Hopeless?

In the last week, how often have you

felt (OWN EQUIVALENT)? Every day? All day?

Have you been crying at all?

(1-4) How long have you been feeling this way?

0	Absent
1	Indicated only on questioning
2	Spontaneously reported verbally
3	Communicated non-verbally (facial expression, posture, voice, tendency to weep)
4	Virtually only communicates about being depressed (spontaneous verbal and non verbal communication)

---

2. Work & Activities

How have you been spending your time this past week?

Have you felt interested in doing (those things) or do

you feel you have to push yourself to do them?

Have you stopped doing anything you used to do?

(Y) Why?

Is there anything you look forward to?

(At Follow-up : Has your interest come back to normal?)

0	No difficulty
1	Thoughts and feelings of incapacity, fatigue, weakness related to activities, work or hobbies (MORE than 3h DAY)
2	Loss of interest in activity by direct report OR indirectly feeling she has to push herself (MORE than 3h DAY)
3	Decreased ACTUAL time spent or productivity (Less than 3hrs at groups or work)
4	bed rest in hospital OR only watching TV without living the ward Stopped working, no activities at home except TV

---

3. Somatic Symptoms (GI)

What has your appetite been this past week?

(What about compared to your usual appetite?)

0	No loss of appetite
1	Loss of appetite but eating without encouragement
2	Difficulty eating without urging

---

4. Somatic symptoms (Gen)

How has your energy been this past week?

Have you been tired all the time?

This week, have you had any backaches, headaches, muscle aches ?

This week, have you felt any heaviness in your limbs, back or head?

0	None
1	Loss of energy OR FATIGUE OR Heaviness in limbs/back/head or non-specific symptom
2	PAIN OR Any clear-cut symptom (Something the patient can point to)

---

5. Weight Loss

Have you lost any weight since this past week?

(Y) How much?

Do you think your clothes are any looser on you?

At F/up : Have you gained any of the weight back?

0	Less than 1lb loss in week
1	More than 1lb loss in week
2	More than 2lb loss in week

---

6. Genital Symptoms (Libido)

How has your interest been in sex this week?

Has there been any change in your interest in sex

from when you were not depressed?

Is it something you have thought about much?

(NO) Is that unusual for you?

0	Absent
1	Mild
2	Severe

7. Insomnia Early

How have you been sleeping over the last week?

Have you had any trouble falling asleep at the beginning of the night?

(Y) Right after you go to bed, how long has it taken you to fall asleep?

How many nights this week have you had trouble falling asleep?

0	No difficulty falling asleep
1	Complains of occasional difficulty falling asleep (>1/2 an hour) 3 OR LESS NIGHTS
2	Complains of *nightly* difficulty falling asleep 4 OR MORE NIGHTS

---

8. Insomnia Middle (UP TO 4 A.M)

During the past week, have you been waking up

in the middle of the night? (Y) Do you get out of bed?

What do you do? (Only go to the bathroom?)

When you get back to bed, are you able to fall right back asleep?

Have you felt your sleeping has been restless or disturbed some nights?

0	Absent or habitual waking only to void bladder
1	Wakes once or twice during the night but falls asleep again without undue delay
2	Wakes frequently OR wakes occasionally but has difficulty (more1/2hr) falling asleep again

---

9. Insomnia late (BEFORE 6H/ 1 NIGHT SUFFICIENT)

What time have you been waking up in the morning

for the last time, this past week?

What time do you usually wake up (before you got depressed)?

IF EARLY: Is it the alarm or do you just wake up youself?

0	No difficulty
1	Waking in early hours but goes back to sleep
2	Unable to fall asleep again

---

10. Feelings of Guilt

Have you been especially critical of yourself this past week,

feeling you've done things wrong, or let others down?

(Y) What have your thoughts been?

Have you been feeling guilty about anything that

you've done or not done?

Have you thought that you've brought this illness on yourself in some way?

Do you feel you're being punished by being sick?

0	Absent
1	Self-reproach OR feels he has let people down
2	Ideas of guilt or rumination over past errors or sinful deeds
3	present illness is a punishment.Delusions of guilt
4	hears accusatory or denunciatory voices and/or experiences threatening visual hallucinations

---

11.Suicide

This past week have you had thoughts that

life is not worth living? Or that you'd be better off dead?

What about having thoughts of hurting or even killing yourself?

(Y) What have you thought about?

Have you actually done anything to hurt yourself?

0	Absent
1	Feels life is not worth living
2	Wishes he was dead or any thoughts of possible death to self
3	Suicidal ideas or gesture
4	Attempts at suicide

---

12. Anxiety Psychic

Have you been feeling especially tense or irritable this past week?

Have you been worring a lot about little unimportant things,

things you wouldn't ordinarily worry about?

(Y) Like what, for example?

0	No difficulty
1	Subjective tension and irritability
2	Worrying about minor matters
3	Apprehensive attitude apparent in face or speech
4	Fears expressed without questioning

13. Anxiety Somatic

In this past week, have you had any of these physical symptoms?

Dry mouth__Gas__Indigestion__Diarrhoea__Cramps

Heart Palpitations__Headaches__Hyperventilating__

Having to urinate frequently__Sighing__Sweating

How much have these things been bothering you this past week?

How bad have they gotten? How much of the time, or how often have you got them?

0	Absent
1	Mild — Sx present only occasionally
2	Moderate — Sx present on most days
3	Severe — Sx present all the time
4	Incapacitating

14.Hypochondriasis

In the last week, how much have your thoughts been focussed on your physical health, or how your body is working ?

Do you complain much about how you feel physically?

Have you found yourself asking for help with things that you could really do yourself?

(Y) Like what, for exemple? How often has that happened?

0	Not present
1	Self-absorption
2	Preoccupation with physical health
3	Frequent complaints OR requests for help etc.
4	Hypochondriacal Delusions

---

15. Insight

Based on observation

0	Acknowledges being depressed and ill OR not currently depressed
1	Acknowledges illness but attributes cause to food/climate/overwork/virus/stress, etc.
2	Denies being ill at all

---

16. Psychomotor Retardation

Psychomotor slowing manifested in difficulty speaking, impaired ability to concentrate, decreased motor activity

0	Normal speech and thought
1	Slight retardation at interview or slowed movements
2	Obvious retardation at interview - response time to questions increased
3	Interview difficult to complete
4	*Complete* stupor

---

17. Agitation

Based on observation

0	None
1	Fidgetiness
2	Playing with hands / hair - stays seated
3	Moving about, cannot sit still - gets out of chair
4	Hand wringing, nail biting, hair-pulling, biting of lips

---

18. Diurnal Variation

This past week, have you been feeling better or worse at any particular time of day - morning or evening?

(Y) How much worse do you feel? A little bit ot a lot worse?

A — Time	
0	No variation OR not depressed
1	Worse in AM
2	Worse in PM

B — Severity	
0	None
1	Mild
2	Severe

19. Depersonalization or Derealisation

In the past week, have you ever suddenly had the feeling that

everything is unreal,___ or you're in a dream, ___

or cut off from other people in some strange way?___

(Y) How bad has that been?

(Y) How often this week has that happened?

0	Absent
1	Mild - one event in the last week or recurrent very mild events
2	Moderate - one event per day or sever less frequently
3	Severe - Severe events most days
4	Incapacitating - actually requiring bed rest

---

20. Paranoid symptoms

This past week, have you felt that anyone

was trying to give you a hard time or to hurt you?

(Y) Tell me about it

0	None
1	Suspicious
2	Ideas of reference
3	Delusions of reference or persecution

---

21. Compulsive symptoms

In the past week, have there been things you've had

to do over and over again, like checking the locks on the doors several times?

(Y) Can you give me an example?

0	Absent
1	Mild
2	Severe

---

22. Helplessness

In the past week, did you feel you had trouble coping

with routine activities? Were there times when you felt overwhelmed?

(Y) Were these feelings so bad that you would say you felt helpless?

(Y) Did other people have to urge you to tend to your responsibilities?

Did you need the physical help of others to complete

simple activities like grooming dressing, or eating?

0	Absent
1	Subjective feelings indicated only on questioning
2	Spontaneously reported helpless feelings verbally
3	Objectively requires urging, guidance and reassurance to complete tasks or self-care
4	Objectively requires physical assistance to complete tasks or self-care

---

23. Hopelessness

This past week, were you optimistic or pessimistic about your future?

Do you doubt that things will improve for you ?

(Y) Do you have this doubt all the time?

When people tell you will be well (or stay well), do you feel reassured?

(N) If your doctor told you s/he was optimistic about your prospects, would you feel reassured?

0	Absent
1	Intermittently doubts that things can improve but can be reassured
2	Consistently feels "hopeless" but can be reassured
3	Expresses feelings of discouragement, despair, pessimism, which can't be dispelled
4	Spontaneously reports and inappropriately perseverates feelings of hopelessness

---

24. Worthlessness

During the last week, have you felt that you are

as good as other people whom you know and respect?

Have you felt that others are better than you?

(Y) Did you feel that you are "no good" or "inferior"?

(Y) How often did you feel this way in the past week?

Do feel that you are worth nothing at all, either to yourself or others?

0	Absent
1	Indicates loss of self esteem on questioning
2	Spontaneously indicates Loss of self esteem
3	Volunteers that he is no good or inferior - differs from 2 by degree
4	Delusions of worthlessness

Total score ☐

APPENDIX 6: BECK DEPRESSION INVENTORY-II (BDI-II)

Name: _____ Marital Status: _____ Age: _____ Sex: _____

Occupation: _____ Education: _____

Instructions: This questionnaire consists of 21 groups of statements. Please read each group of statements carefully, and then pick out the **one statement** in each group that best describes the way you have been feeling during the **past two weeks, including today**. Circle the number beside the statement you have picked. If several statements in the group seem to apply equally well, circle the highest number for that group. Be sure that you do not choose more than one statement for any group, including Item 16 (Changes in Sleeping Pattern) or Item 18 (Changes in Appetite).

1. Sadness

0 I do not feel sad.
1 I feel sad much of the time.
2 I am sad all the time.
3 I am so sad or unhappy that I can't stand it.

2. Pessimism

0 I am not discouraged about my future.
1 I feel more discouraged about my future than I used to be.
2 I do not expect things to work out for me.
3 I feel my future is hopeless and will only get worse.

3. Past Failure

0 I do not feel like a failure.
1 I have failed more than I should have.
2 As I look back, I see a lot of failures.
3 I feel I am a total failure as a person.

4. Loss of Pleasure

0 I get as much pleasure as I ever did from the things I enjoy.
1 I don't enjoy things as much as I used to.
2 I get very little pleasure from the things I used to enjoy.
3 I can't get any pleasure from the things I used to enjoy.

5. Guilty Feelings

0 I don't feel particularly guilty.
1 I feel guilty over many things I have done or should have done.
2 I feel quite guilty most of the time.
3 I feel guilty all of the time.

6. Punishment Feelings

0 I don't feel I am being punished.
1 I feel I may be punished.
2 I expect to be punished.
3 I feel I am being punished.

7. Self-Dislike

0 I feel the same about myself as ever.
1 I have lost confidence in myself.
2 I am disappointed in myself.
3 I dislike myself.

8. Self-Criticalness

0 I don't criticize or blame myself more than usual.
1 I am more critical of myself than I used to be.
2 I criticize myself for all of my faults.
3 I blame myself for everything bad that happens.

9. Suicidal Thoughts or Wishes

0 I don't have any thoughts of killing myself.
1 I have thoughts of killing myself, but I would not carry them out.
2 I would like to kill myself.
3 I would kill myself if I had the chance.

10. Crying

0 I don't cry anymore than I used to.
1 I cry more than I used to.
2 I cry over every little thing.
3 I feel like crying, but I can't.

_____ Subtotal Page 1

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11. Agitation

0 I am no more restless or wound up than usual.

1 I feel more restless or wound up than usual.

2 I am so restless or agitated that it's hard to stay still.

3 I am so restless or agitated that I have to keep moving or doing something.

12. Loss of Interest

0 I have not lost interest in other people or activities.

1 I am less interested in other people or things than before.

2 I have lost most of my interest in other people or things.

3 It's hard to get interested in anything.

13. Indecisiveness

0 I make decisions about as well as ever.

1 I find it more difficult to make decisions than usual.

2 I have much greater difficulty in making decisions than I used to.

3 I have trouble making any decisions.

14. Worthlessness

0 I do not feel I am worthless.

1 I don't consider myself as worthwhile and useful as I used to.

2 I feel more worthless as compared to other people.

3 I feel utterly worthless.

15. Loss of Energy

0 I have as much energy as ever.

1 I have less energy than I used to have.

2 I don't have enough energy to do very much.

3 I don't have enough energy to do anything.

16. Changes in Sleeping Pattern

0 I have not experienced any change in my sleeping pattern.

1a I sleep somewhat more than usual.

1b I sleep somewhat less than usual.

2a I sleep a lot more than usual.

2b I sleep a lot less than usual.

3a I sleep most of the day.

3b I wake up 1–2 hours early and can't get back to sleep.

17. Irritability

0 I am no more irritable than usual.

1 I am more irritable than usual.

2 I am much more irritable than usual.

3 I am irritable all the time.

18. Changes in Appetite

0 I have not experienced any change in my appetite.

1a My appetite is somewhat less than usual.

1b My appetite is somewhat greater than usual.

2a My appetite is much less than before.

2b My appetite is much greater than usual.

3a I have no appetite at all.

3b I crave food all the time.

19. Concentration Difficulty

0 I can concentrate as well as ever.

1 I can't concentrate as well as usual.

2 It's hard to keep my mind on anything for very long.

3 I find I can't concentrate on anything.

20. Tiredness or Fatigue

0 I am no more tired or fatigued than usual.

1 I get more tired or fatigued more easily than usual.

2 I am too tired or fatigued to do a lot of the things I used to do.

3 I am too tired or fatigued to do most of the things I used to do.

21. Loss of Interest in Sex

0 I have not noticed any recent change in my interest in sex.

1 I am less interested in sex than I used to be.

2 I am much less interested in sex now.

3 I have lost interest in sex completely.

9 10 11 12 A B C D E

_____ Subtotal Page 2

_____ Subtotal Page 1

APPENDIX 7: BRIEF PSYCHIATRIC RATING SCALE (BPRS)

	BPRS	Absent	Very Mild	Mild	Moderate	Moderate Severe	Severe	Extreme
1.	Somatic Concern	1	2	3	4	5	6	7
2.	Anxiety	1	2	3	4	5	6	7
3.	Emotional Withdrawal	1	2	3	4	5	6	7
4.	Conceptual Disorganisation	1	2	3	4	5	6	7
5.	Guilt	1	2	3	4	5	6	7
6.	Tension	1	2	3	4	5	6	7
7.	Mannerisms & Posturing	1	2	3	4	5	6	7
8.	Grandiosity	1	2	3	4	5	6	7
9.	Depression	1	2	3	4	5	6	7
10.	Hostility	1	2	3	4	5	6	7
11.	Suspiciousness	1	2	3	4	5	6	7
12.	Hallucinations	1	2	3	4	5	6	7
13.	Motor Retardation	1	2	3	4	5	6	7
14.	Uncooperativeness	1	2	3	4	5	6	7
15.	Unusual Thought Content	1	2	3	4	5	6	7
16.	Blunted Affect	1	2	3	4	5	6	7
17.	Excitement	1	2	3	4	5	6	7
18.	Disorientation	1	2	3	4	5	6	7

BPRS Total:	

APPENDIX 8: NATIONAL ADULT READING TEST (NART)

Appendix I.1: Pronunciation guide

CHORD	kôrd	SUPERFLUOUS	sōō-pûr'flŏŏ-əs, sŭ-pûr'flŏŏ-əs
ACHE	āk	SIMILE	sim'i-li
DEPOT	dep'ō	BANAL	bən-al'
AISLE	īl	QUADRUPED	kwod'rŏŏ-ped
BOUQUET	bōōk'a, bōōkā', bōkā'	CELLIST	chel'ist
PSALM	säm	FACADE	fa-säd'
CAPON	kā'pn	ZEALOT	zel'ət
DENY	di-nī	DRACHM	dram
NAUSEA	nô'si-ə,nô'zhə	AEON	ē'on
DEBT	det	PLACEBO	plə-sē'bō
COURTEOUS	kûrt'yəs	ABSTEMIOUS	ab-stē'mi'əs
RAREFY	râr'-i-fī	DETENTE	dā-tät (Fr.)
EQUIVOCAL	i-kwiv'ə-kl	IDYLL	id'il, id'əl
NAIVE	nä-ēv	PUERPERAL	pū-ûr'pər-əl
CATACOMB	kat'ə-kōōm	AVER	ə-vûr'
GAOLED	jāld	GAUCHE	gō sh
THYME	tīm	TOPIARY	tō'pi-ə-ri
HEIR	âr	LEVIATHAN	le-vī'ə-thən
RADIX	rā'diks	BEATIFY	bi-at'i-fi
ASSIGNATE	as'-ig-nāt	PRELATE	prel'it
HIATUS	hī-ā'təs	SIDEREAL	sī-dē'ri-əl
SUBTLE	sut'l	DEMESNE	di-mān', di-mēn'
PROCREATE	prō'kri-āt	SYNCOPE	sing'kə-pē
GIST	jist	LABILE	lā'bil
GOUGE	gowj	CAMPANILE	kam-pən-ē'lā, kam-pən-ē'lē

APPENDIX 9: ADDENBROOKE'S COGNITIVE EXAMINATION REVISED (ACER)

ADDENBROOKE'S COGNITIVE EXAMINATION - ACE-R

Final Revised Version A (2005)

Name :
Date of birth :
Hospital no. :

Addressograph

Date of testing: ..... /..... /.....
Tester's name: .....
Age at leaving full-time education: .....
Occupation: .....
Handedness: .....

ORIENTATION — ATTENTION & ORIENTATION

➢ Ask: What is the	Day	Date	Month	Year	Season	[Score 0-5]
➢ Ask: Which	Building	Floor	Town	County	Country	[Score 0-5]

REGISTRATION — ATTENTION & ORIENTATION

➢ Tell: 'I'm going to give you three words and i'd like you to repeat after me: lemon, key and ball'. After subject repeats, say 'Try to remember them because i'm going to ask you later'. Score only the first trial (repeat 3 times if necessary).

Register number of trials .....

[Score 0-3]

ATTENTION & CONCENTRATION — ATTENTION & ORIENTATION

➢ Ask the subject: ' could you take 7 away from a 100? After the subject responds, ask him or her to take away another 7 to a total of 5 subtractions. If subject make a mistake, carry on and check the subsequent answer (i.e. 93, 84, 77, 70, 63 -score 4)

Stop after five subtractions (93, 86, 79, 72, 65). ....

➢ Ask: 'could you please spell **WORLD** for me? Then ask him/her to spell it backwards:

....

[Score 0-5] (for the best performed task)

MEMORY - Recall — MEMORY

➢ Ask: 'Which 3 words did I ask you to repeat and remember?'

....

[Score 0-3]

MEMORY - Anterograde Memory — MEMORY

➢ Tell: ' I'm going to give you a name and address and I'd like you to repeat after me. We'll be doing that 3 times, so you have a chance to learn it. I'll be asking you later'

Score only the third trial

[Score 0-7]

	1st Trial	2nd Trial	3rd Trial
Harry Barnes	....	....	....
73 Orchard Close	....	....	....
Kingsbridge	.....	.....	.....
Devon	.....	.....	.....

MEMORY - Retrograde Memory — MEMORY

➢ Name of current Prime Minister .....
➢ Name of the woman who was Prime Minister .....
➢ Name of the USA president .....
➢ Name of the USA president who was assassinated in the 1960's .....

[Score 0 -4]

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VERBAL FLUENCY - Letter 'P' and animals

➢ **Letters**

Say: 'I'm going to give you a letter of the alphabet and I'd like you to generate as many words as you can beginning with that letter, but not names of people or places. Are you ready? You've got a minute and the letter is P'

[Score 0 - 7] ☐

>17	7
14-17	6
11-13	5
8-10	4
6-7	3
4-5	2
2-3	1
<2	0
total	correct

➢ **Animals**

Say: 'Now can you name as many animals as possible, beginning with any letter?

[Score 0 - 7] ☐

>21	7
17-21	6
14-16	5
11-13	4
9-10	3
7-8	2
5-6	1
<5	0
total	correct

FLUENCY

LANGUAGE - Comprehension

➢ Show written instruction:

[Score 0-1] ☐ ☐

Close your eyes

➢ 3 stage command:
'Take the paper in your right hand. Fold the paper in half. Put the paper on the floor'

[Score 0-3] ☐ ☐

LANGUAGE - Writing

➢ Ask the subject to make up a sentence and write it in the space below:
Score 1 if sentence contains a subject and a verb (see guide for examples)

[Score 0-1] ☐ ☐

LANGUAGE

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LANGUAGE - Repetition

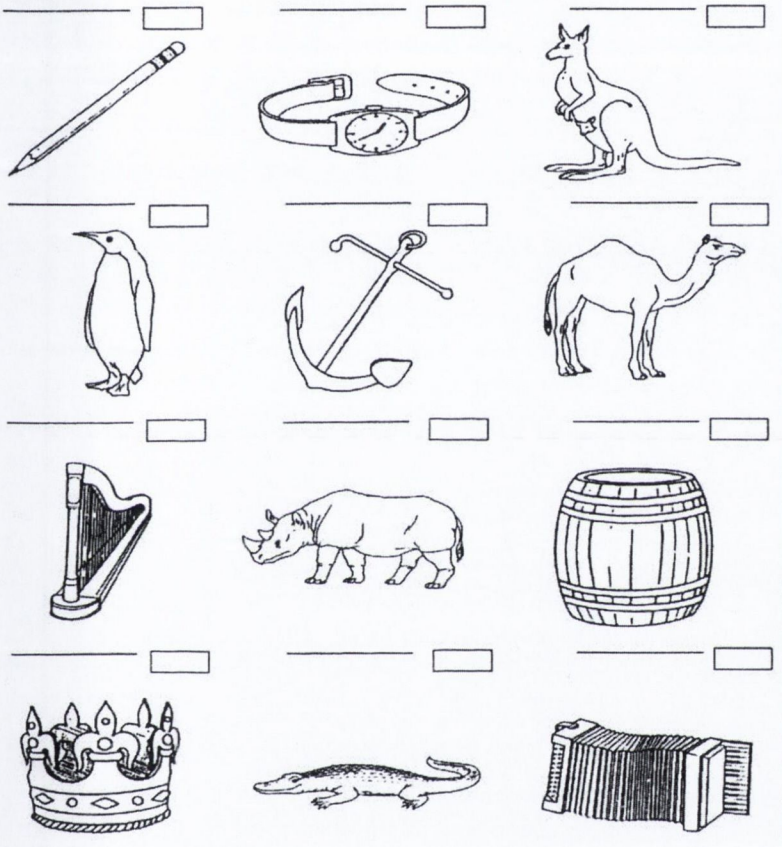
➢ Ask the subject to repeat: **' hippopotamus'; 'eccentricity; 'unintelligible'; 'statistician'** [Score 0-2]
Score 2 if all correct; 1 if 3 correct; 0 if 2 or less.

➢ Ask the subject to repeat: **'Above, beyond and below'** [Score 0-1]

➢ Ask the subject to repeat: **'No ifs, ands or buts'** [Score 0-1]

LANGUAGE - Naming

➢ Ask the subject to name the following pictures: [Score 0-2] pencil + watch



[Score 0-10]

LANGUAGE - Comprehension

➢ Using the pictures above, ask the subject to: [Score 0-4]

- Point to the one which is associated with the monarchy _____
- Point to the one which is a marsupial _____
- Point to the one which is found in the Antarctic _____
- Point to the one which has a nautical connection _____

LANGUAGE

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ADDENBROOKE'S COGNITIVE EXAMINATION - ACE-R *Final Revised Version (2005)*

LANGUAGE - Reading

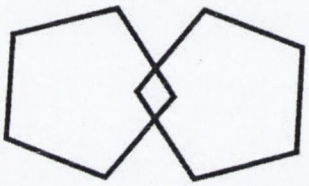
➢ Ask the subject to read the following words: [Score 1 only if all correct] [Score 0-1]

sew
pint
soot
dough
height

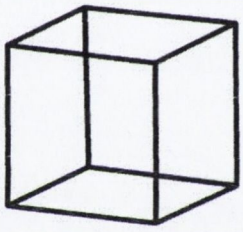
LANGUAGE

VISUOSPATIAL ABILITIES

➢ Overlapping pentagons: Ask the subject to copy this diagram: [Score 0-1]



➢ Wire cube : Ask the subject to copy this drawing (for scoring, see instructions guide) [Score 0-2]



➢ Clock: Ask the subject to draw a clock face with numbers and the hands at ten past five. (for scoring see instruction guide: circle = 1, numbers = 2, hands = 2 if all correct) [Score 0-5]

VISUOSPATIAL

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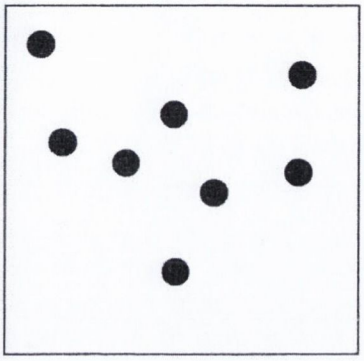
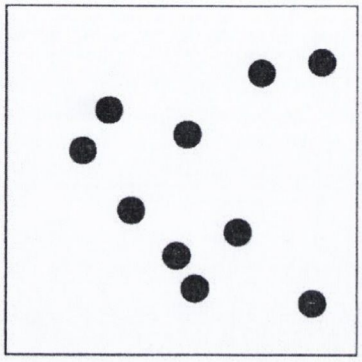
PERCEPTUAL ABILITIES

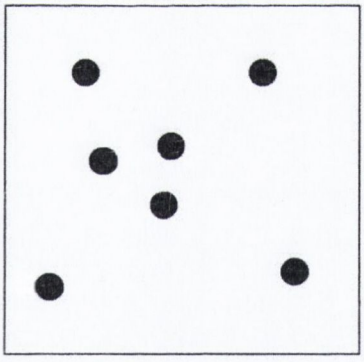
VISUOSPATIAL

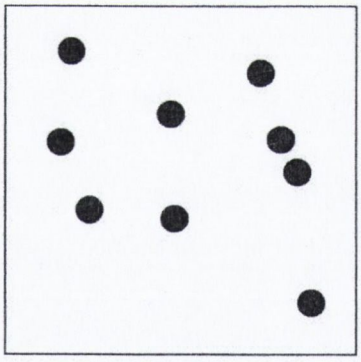
➢ Ask the subject to count the dots without pointing them

[Score 0-4]









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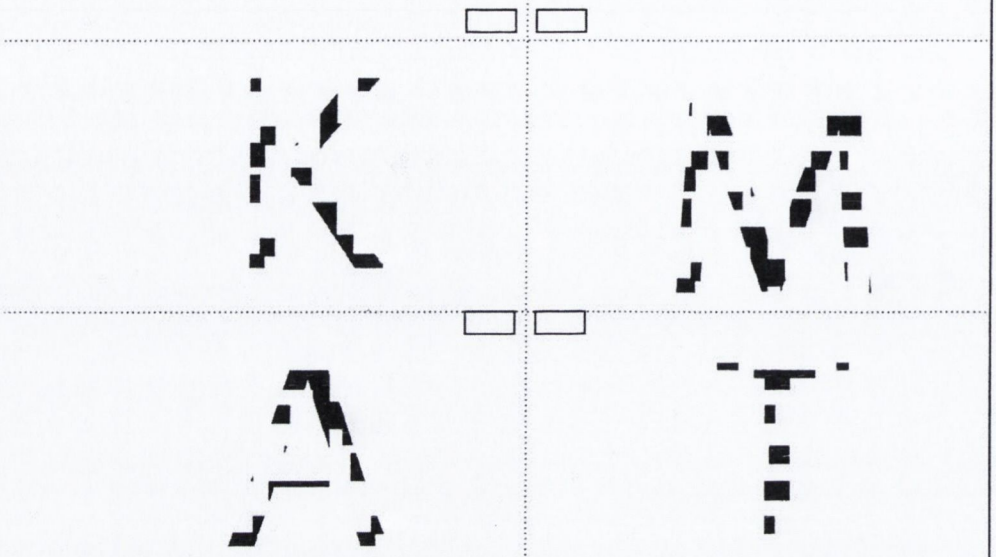
ADDENBROOKE'S COGNITIVE EXAMINATION - ACE-R

Final Revised Version A (2005)

PERCEPTUAL ABILITIES

➢ Ask the subject to identify the letters [Score 0-4]



VISUOSPATIAL

RECALL

➢ Ask "Now tell me what you remember of that name and address we were repeating at the beginning"

		[Score 0-7]
Harry Barnes	....	
73 Orchard Close	....	
Kingsbridge	.....	
Devon	.....	

RECOGNITION

➢ This test should be done if subject failed to recall one or more items. If all items were recalled, skip the test and score 5. If only part is recalled start by ticking items recalled in the shadowed column on the right hand side. Then test not recalled items by telling "ok, I'll give you some hints: was the name X, Y or Z?" and so on. Each recognised item scores one point which is added to the point gained by recalling. [Score 0-5]

Jerry Barnes		Harry Barnes		Harry Bradford		recalled	
37		73		76		recalled	
Orchard Place		Oak Close		Orchard Close		recalled	
Oakhampton		Kingsbridge		Dartington		recalled	
Devon		Dorset		Somerset		recalled	

MEMORY

General Scores

MMSE	/30
ACE-R	/100

Subscores

Attention and Orientation	/18
Memory	/26
Fluency	/14
Language	/26
Visuospatial	/16

SCORE

Normative values based on 63 controls aged 52-75 and 142 dementia patients aged 46-86

Cut-off <88 gives 94% senstivity and 89% specificity for dementia
Cut-off <82 gives 84% sensitivity and 100% specificity for dementia

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APPENDIX 10: AUTOBIOGRAPHICAL MEMORY INTERVIEW

Autobiographical Memory Interivew–Short Form

PART 1: FAMILY MEMBER (1)

Interviewer: You will begin this section by asking the subject to name a relative about whom five questions will be asked. If several relatives are mentioned, ask regarding the relative with whom the subject has the most frequent contact. If the subject has no relative, ask regarding his/her closest friend.

I AM GOING TO ASK YOU SOME QUESTIONS ABOUT A FAMILY MEMBER: WHAT IS THE FIRST AND NAME OF THE RELATIVE WHO IS THE MOST IMPORTANT TO YOU BUT WHO DOES NOT LIVE WITH

NOTES:

PRE: name provided	POST: name provided

NOTES:

WHAT IS HIS/HER RELATION TO YOU

NOTES:

PRE: relationship

Interviewer: At POST, if the name recalled is different than the name given at PRE, remind the subject of the original name and relation, and proceed with questions 1-5.

QUESTION 1: WHAT IS THE MONTH AND DAY OF HIS/HER BIRTHDAY?

NOTES:

PRE: month & day	score	POST: month & day	score

QUESTION 2: WHAT WAS HIS/HER AGE AT THE TIME YOU ENTERED THIS PROGRAM?

NOTES:

PRE: age	score	POST: age	score

QUESTION 3: WHAT WAS HIS/HER COMPLETE ADDRESS AT THE TIME YOU ENTERED THIS PRI

NOTES:

PRE: address (number, street, & apt.)	score	POST: address (number, street, & apt.)	score
city: state:		city: state:	
zip code:		zip code:	

QUESTION 4: WHAT WAS HIS/HER PHONE NUMBER WITH AREA CODE AT THE TIME YOU ENTERED PROGRAM?

NOTES:

PRE: phone number	score	POST: phone number	score

QUESTION 5: LIST THE FULL NAMES OF THE PERSON OR PERSONS LIVING WITH YOUR RELATIV TIME YOU ENTERED THIS PROGRAM?

NOTES:

PRE: house mates	score	POST: house mates	score

PRE: total score	POST: total score

PAGE 1

PART 1: FAMILY MEMBER (2)

Interviewer: You will begin this section by asking the subject to name a relative about whom five questions will be asked. If several relatives are mentioned, ask regarding the relative with whom the subject has the most frequent contact. If the subject has no relative, ask regarding his/her closest friend.

I AM GOING TO ASK YOU SOME QUESTIONS ABOUT A FAMILY MEMBER: WHAT IS THE FIRST AND NAME OF THE RELATIVE WHO IS THE MOST IMPORTANT TO YOU BUT WHO DOES NOT LIVE WITH

3 MOS POST: name provided	6 MOS POST: name provided	9 MOS POST: name provided
NOTES:	NOTES:	NOTES:

*Interviewer: At **all** POST testing sessions, if the name recalled is different than the name given at PRE, remind the subject of the original name and relation provided, and proceed with questions 1-5.*

QUESTION 1: WHAT IS THE MONTH AND DAY OF HIS/HER BIRTHDAY?

3 MOS POST: month & day	score	6 MOS POST: month & day	score	9 MOS POST: month & day	score

QUESTION 2: WHAT WAS HIS/HER AGE AT THE TIME YOU ENTERED THIS PROGRAM?

3 MOS POST: age	score	6 MOS POST: age	score	9 MOS POST: age	score

QUESTION 3: WHAT WAS HIS/HER COMPLETE ADDRESS AT THE TIME YOU ENTERED THIS PR(

3 MOS POST: address	score	6 MOS POST: address	score	9 MOS POST: address	score
number, street, & apt. #		number, street, & apt. #		number, street, & apt. #	
city: state:		city: state:		city: state:	
zip code:		zip code:		zip code:	

QUESTION 4: WHAT WAS HIS/HER PHONE NUMBER WITH AREA CODE AT THE TIME YOU ENTERED PROGRAM?

3 MOS POST: phone number	score	6 MOS POST: phone number	score	9 MOS POST: phone number	score

QUESTION 5: LIST THE FULL NAMES OF THE PERSON OR PERSONS LIVING WITH YOUR RELATIV TIME YOU ENTERED THIS PROGRAM?

3 MOS POST: house mates	score	6 MOS POST: house mates	score	9 MOS POST: house mates	score

3 MOS POST: total score	6 MOS POST: total score	9 MOS POST: total score

PAGE 2

PART 2: TRAVEL (3)

Interviewer: You will begin this section by asking the subject to recall the LAST major trip that he/she took before entering the program. If the subject has never traveled farther than 100 miles, ask regarding the most recent overnight trip away from home.

I AM GOING TO ASK YOU SOME QUESTIONS ABOUT THE LAST MAJOR TRIP YOU TOOK BEFORE YOU ENTERED THIS PROGRAM: WHERE DID YOU GO ON YOUR LAST OVERNIGHT TRIP OF 100 MI OR MORE AWAY FROM HOME?

NOTES:

PRE: trip destination	POST: trip destination

NOTES:

IN WHAT MONTH AND YEAR DID YOU TAKE THIS TRI

NOTES:

PRE: month & year of trip

Interviewer: At POST, if the trip recalled is different than the trip given at PRE, remind the subject of the original trip and date, and proceed with questions 1-5.

QUESTION 1: COUNTING THE DAYS YOU SPENT TRAVELING, HOW MANY DAYS WERE YOU AWA

NOTES:

PRE: days away	score	POST: days away	score

QUESTION 2: WHAT IS THE FULL NAME OF THE HOTEL AT WHICH (OR PERSON WITH WHOM) YOU STAYED DURING THE MAJORITY OF THIS TRIP?

NOTES:

PRE: name of lodging	score	POST: name of lodging	score

QUESTION 3: LIST THE FULL NAMES OF THE PERSON OR PERSONS WHO WENT WITH YOU ON T

NOTES:

PRE: travel companion(s)	score	POST: travel companion	score

QUESTION 4: WHAT WAS THE MAIN REASON FOR TAKING THIS TRIP?

NOTES:

PRE: reason for trip	score	POST: reason for trip	score

QUESTION 5: WHAT DID YOU ENJOY MOST ABOUT THIS TR

NOTES:

PRE: enjoyed about trip	score	POST: enjoyed about trip	score

PRE: total score	POST: total score

Page 3

PART 2: TRAVEL (4)

Interviewer: You will begin this section by asking the subject to recall the LAST major trip that he/she took before entering the program. If the subject has never traveled farther than 100 miles, ask regarding the most recent overnight trip away from home.

I AM GOING TO ASK YOU SOME QUESTIONS ABOUT THE LAST MAJOR TRIP YOU TOOK BEFORE YOU ENTERED THIS PROGRAM: WHERE DID YOU GO ON YOUR LAST OVERNIGHT TRIP OF 100 MI OR MORE AWAY FROM HOME?

3 MOS POST: trip destination	6 MOS POST: trip destination	9 MOS POST: trip destination
NOTES:	NOTES:	NOTES:

Interviewer: At all POST testing sessions, if the trip recalled is different than the trip given at PRE, remind the subject of the original trip and date provided, and proceed with questions 1-5.

QUESTION 1: COUNTING THE DAYS YOU SPENT TRAVELING, HOW MANY DAYS WERE YOU AWA

3 MOS POST: days away	score	6 MOS POST: days away	score	9 MOS POST: days away	score

QUESTION 2: WHAT IS THE FULL NAME OF THE HOTEL AT WHICH (OR PERSON WITH WHOM) YOU STAYED DURING THE MAJORITY OF THIS TRIP?

3 MOS POST: name of lodging	score	6 MOS POST: name of lodging	score	9 MOS POST: name of lodging	score

QUESTION 3: LIST THE FULL NAMES OF THE PERSON OR PERSONS WHO WENT WITH YOU ON T

3 MO POST: travel companion(s)	score	6 MO POST: travel companion(s)	score	9 MO POST: travel companion	score

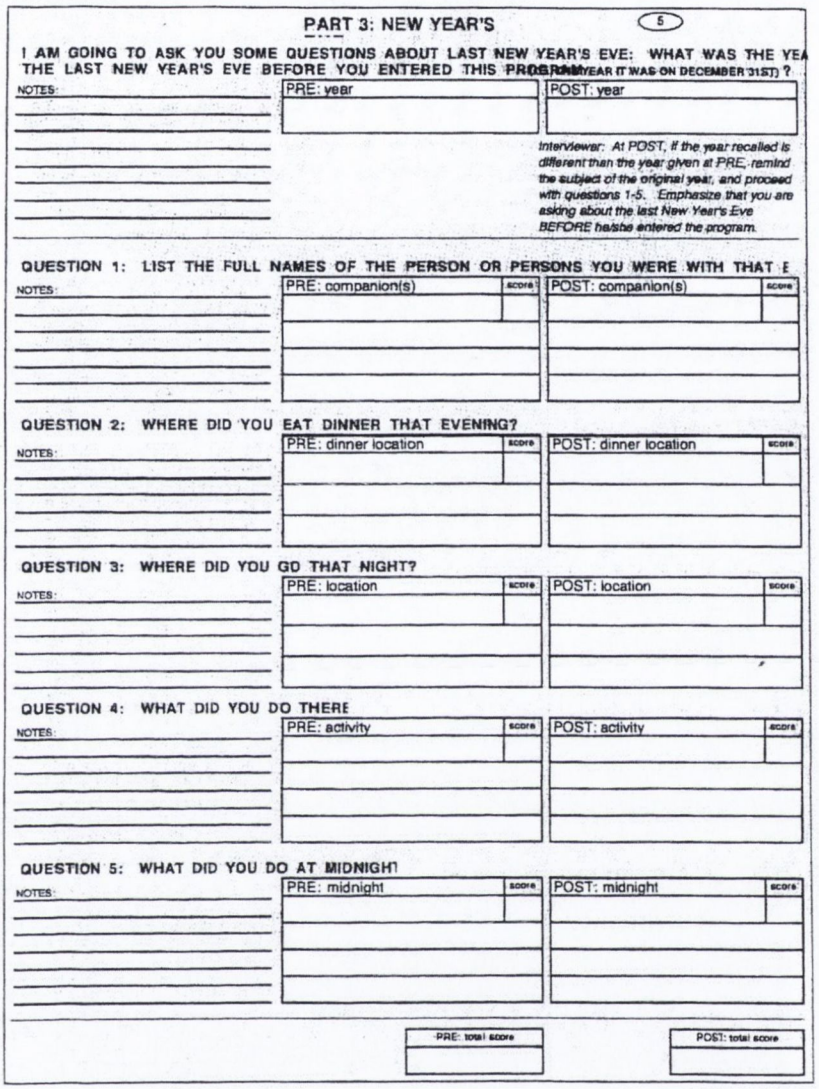
QUESTION 4: WHAT WAS THE MAIN REASON FOR TAKING THIS TRIP?

3 MOS POST: reason for trip	score	6 MOS POST: reason for trip	score	9 MOS POST: reason for trip	score

QUESTION 5: WHAT DID YOU ENJOY MOST ABOUT THIS TR

3 MO POST: enjoyed about trip	score	6 MO POST: enjoyed about trip	score	9 MO POST: enjoyed about trip	score

3 MOS POST: total score	6 MOS POST: total score	9 MOS POST: total score



PART 3: NEW YEAR'S

5

I AM GOING TO ASK YOU SOME QUESTIONS ABOUT LAST NEW YEAR'S EVE: WHAT WAS THE YEA
THE LAST NEW YEAR'S EVE BEFORE YOU ENTERED THIS PROGRAM? (THAT YEAR IT WAS ON DECEMBER 31ST) ?

NOTES:

PRE: year	POST: year

Interviewer: At POST, if the year recalled is different than the year given at PRE, remind the subject of the original year, and proceed with questions 1-5. Emphasize that you are asking about the last New Year's Eve BEFORE he/she entered the program.

QUESTION 1: LIST THE FULL NAMES OF THE PERSON OR PERSONS YOU WERE WITH THAT E

NOTES:

PRE: companion(s)	score	POST: companion(s)	score

QUESTION 2: WHERE DID YOU EAT DINNER THAT EVENING?

NOTES:

PRE: dinner location	score	POST: dinner location	score

QUESTION 3: WHERE DID YOU GO THAT NIGHT?

NOTES:

PRE: location	score	POST: location	score

QUESTION 4: WHAT DID YOU DO THERE

NOTES:

PRE: activity	score	POST: activity	score

QUESTION 5: WHAT DID YOU DO AT MIDNIGHT

NOTES:

PRE: midnight	score	POST: midnight	score

PRE: total score	POST: total score

Page 5

PART 3: NEW YEAR'S

(6)

I AM GOING TO ASK YOU SOME QUESTIONS ABOUT LAST NEW YEAR'S EVE: WHAT WAS THE YE[AR] THE LAST NEW YEAR'S EVE BEFORE YOU ENTERED THIS PROGRAM (THE YEAR IT WAS ON DECEMBER 31ST)?

3 MOS POST: year	6 MOS POST: year	12 MOS POST: year

NOTES: NOTES: NOTES:

Interviewer: At all POST testing sessions, if the year recalled is different than the year given at PRE, remind the subject of the original year, and proceed with questions 1-5. Emphasize that you are asking about the last New Year's Eve BEFORE he/she entered the program, and not necessarily the most recent New Year's Eve.

QUESTION 1: LIST THE FULL NAMES OF THE PERSON OR PERSONS YOU WERE WITH THAT E

3 MOS POST: companion(s)	score	6 MOS POST: companion(s)	score	12 MOS POST: companion(s)	score

QUESTION 2: WHERE DID YOU EAT DINNER THAT EVENING?

3 MOS POST: dinner location	score	6 MOS POST: dinner location	score	12 MOS POST: dinner location	score

QUESTION 3: WHERE DID YOU GO THAT NIGHT?

3 MOS POST: location	score	6 MOS POST: location	score	12 MOS POST: location	score

QUESTION 4: WHAT DID YOU DO THERE

3 MOS POST: activity	score	6 MOS POST: activity	score	12 MOS POST: activity	score

QUESTION 5: WHAT DID YOU DO AT MIDNIGHT

3 MOS POST: midnight	score	6 MOS POST: midnight	score	12 MOS POST: midnight	score

3 MOS POST: total score	6 MOS POST: total score	12 MOS POST: total score

Page 6

PART 4: BIRTHDAY (7)

I AM GOING TO ASK YOU SOME QUESTIONS ABOUT YOUR BIRTHDAY: WHAT IS THE DATE OF YOUR BIRTH (MONTH/DAY/YEAR) ?

NOTES:

PRE: birth date (mo/dy/yr)	POST: birth date (mo/dy/yr)

HOW OLD DID YOU BECOME ON YOUR LAST BIRTHDAY BEFORE I ENTERED THIS PROGRAM?

NOTES:

PRE: age

NOTES:

Interviewer: At POST, if the age recalled is different than the age given at PRE, remind the subject of the original age, and proceed with questions 1-5.

QUESTION 1: LIST THE FULL NAMES OF THE PERSON OR PERSONS WHO HELPED CELEBRATE ON YOUR LAST BIRTHDAY:

NOTES:

PRE: companion(s)	score	POST: companion(s)	score

QUESTION 2: WHERE DID YOU CELEBRATE YOUR BIRTHDAY?

NOTES:

PRE: location	score	POST: location	score

QUESTION 3: WHAT DID YOU DO THERE

NOTES:

PRE: activity	score	POST: activity	score

QUESTION 4: FROM WHOM DID YOU RECEIVE GIFTS (IF NO GIFTS, ASK REGARDING CARDS)

NOTES:

PRE: received gifts from	score	POST: received gifts from	score

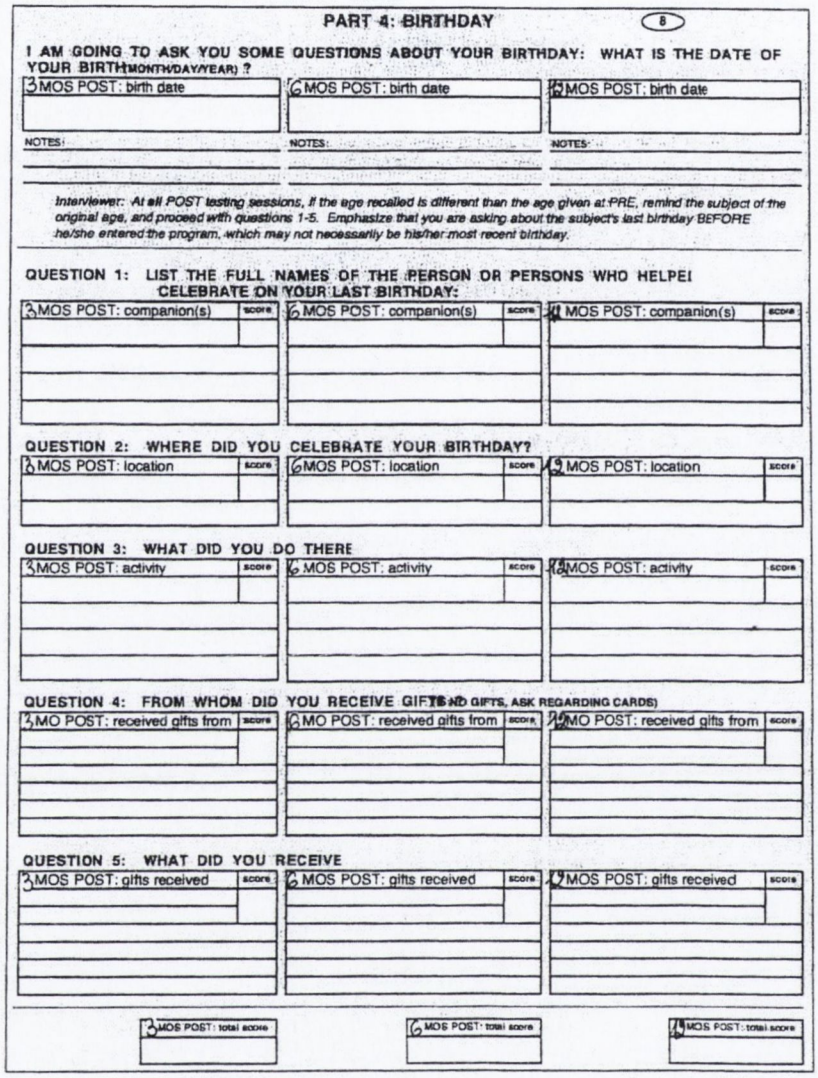
QUESTION 5: WHAT DID YOU RECEIVE

NOTES:

PRE: gifts received	score	POST: gifts received	score

PRE: total score	POST: total score

Page 7



PART 4: BIRTHDAY (8)

I AM GOING TO ASK YOU SOME QUESTIONS ABOUT YOUR BIRTHDAY: WHAT IS THE DATE OF YOUR BIRTH(MONTH/DAY/YEAR) ?

3MOS POST: birth date	6MOS POST: birth date	12MOS POST: birth date
NOTES:	NOTES:	NOTES:

Interviewer: At all POST testing sessions, if the age recalled is different than the age given at PRE, remind the subject of the original age, and proceed with questions 1-5. Emphasize that you are asking about the subject's last birthday BEFORE he/she entered the program, which may not necessarily be his/her most recent birthday.

QUESTION 1: LIST THE FULL NAMES OF THE PERSON OR PERSONS WHO HELPED CELEBRATE ON YOUR LAST BIRTHDAY:

3MOS POST: companion(s)	score	6MOS POST: companion(s)	score	12MOS POST: companion(s)	score

QUESTION 2: WHERE DID YOU CELEBRATE YOUR BIRTHDAY?

3MOS POST: location	score	6MOS POST: location	score	12MOS POST: location	score

QUESTION 3: WHAT DID YOU DO THERE

3MOS POST: activity	score	6MOS POST: activity	score	12MOS POST: activity	score

QUESTION 4: FROM WHOM DID YOU RECEIVE GIFTS (IF NO GIFTS, ASK REGARDING CARDS)

3MO POST: received gifts from	score	6MO POST: received gifts from	score	12MO POST: received gifts from	score

QUESTION 5: WHAT DID YOU RECEIVE

3MOS POST: gifts received	score	6MOS POST: gifts received	score	12MOS POST: gifts received	score

3MOS POST: total score	6MOS POST: total score	12MOS POST: total score

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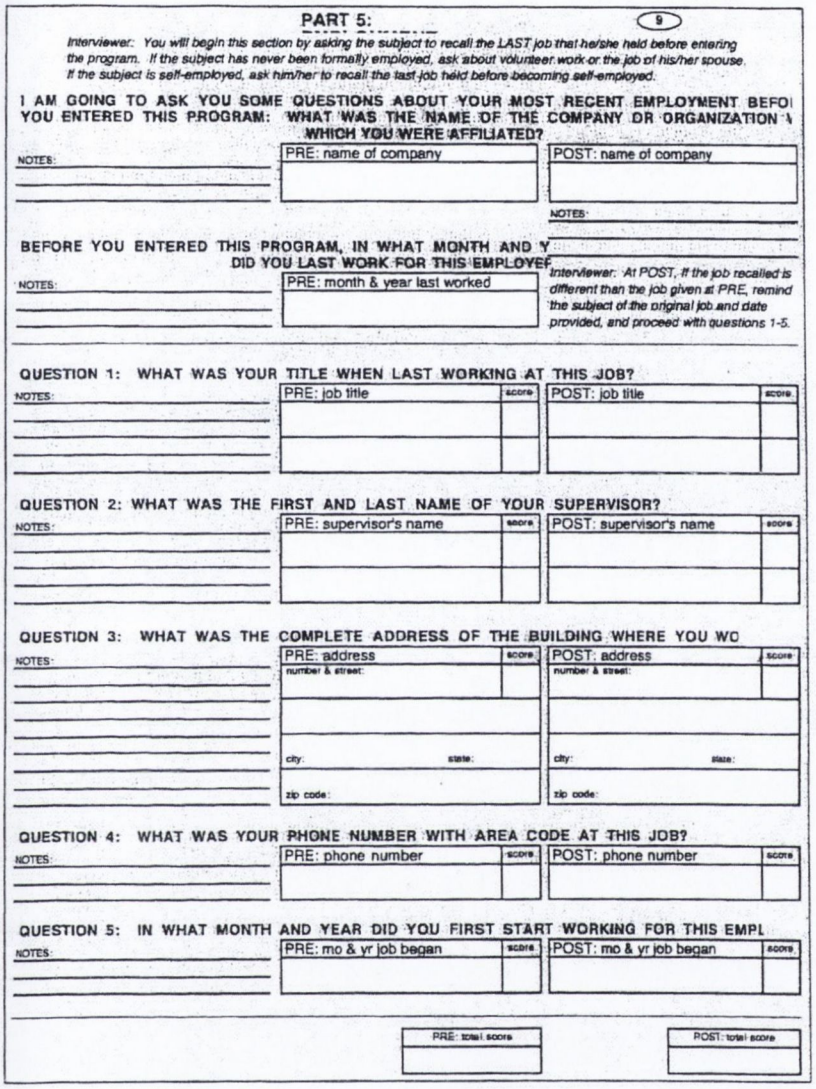


PART 5: [illegible] (9)

Interviewer: You will begin this section by asking the subject to recall the LAST job that he/she held before entering the program. If the subject has never been formally employed, ask about volunteer work or the job of his/her spouse. If the subject is self-employed, ask him/her to recall the last job held before becoming self-employed.

I AM GOING TO ASK YOU SOME QUESTIONS ABOUT YOUR MOST RECENT EMPLOYMENT BEFOI YOU ENTERED THIS PROGRAM: WHAT WAS THE NAME OF THE COMPANY OR ORGANIZATION \ WHICH YOU WERE AFFILIATED?

NOTES:

PRE: name of company	POST: name of company

NOTES:

BEFORE YOU ENTERED THIS PROGRAM, IN WHAT MONTH AND Y DID YOU LAST WORK FOR THIS EMPLOYE?

NOTES:

PRE: month & year last worked

Interviewer: At POST, if the job recalled is different than the job given at PRE, remind the subject of the original job and date provided, and proceed with questions 1-5.

QUESTION 1: WHAT WAS YOUR TITLE WHEN LAST WORKING AT THIS JOB?

NOTES:

PRE: job title	score	POST: job title	score

QUESTION 2: WHAT WAS THE FIRST AND LAST NAME OF YOUR SUPERVISOR?

NOTES:

PRE: supervisor's name	score	POST: supervisor's name	score

QUESTION 3: WHAT WAS THE COMPLETE ADDRESS OF THE BUILDING WHERE YOU WO

NOTES:

PRE: address	score	POST: address	score
number & street:		number & street:	
city: state:		city: state:	
zip code:		zip code:	

QUESTION 4: WHAT WAS YOUR PHONE NUMBER WITH AREA CODE AT THIS JOB?

NOTES:

PRE: phone number	score	POST: phone number	score

QUESTION 5: IN WHAT MONTH AND YEAR DID YOU FIRST START WORKING FOR THIS EMPL

NOTES:

PRE: mo & yr job began	score	POST: mo & yr job began	score

PRE: total score	POST: total score

Page 9

PART 5: (10)

Interviewer: You will begin this section by asking the subject to recall the LAST job that he/she held before entering the program. If the subject has never been formally employed, ask about volunteer work or the job of his/her spouse. If the subject is self-employed, ask him/her to recall the last job held before becoming self-employed.

I AM GOING TO ASK YOU SOME QUESTIONS ABOUT YOUR MOST RECENT EMPLOYMENT BEFO YOU ENTERED THIS PROGRAM: WHAT WAS THE NAME OF THE COMPANY OR ORGANIZATION V WHICH YOU WERE AFFILIATED?

3 MOS POST: name of company	6 MOS POST: name of company	12 MOS POST: name of company
NOTES:	NOTES:	NOTES:

Interviewer: At all POST testing sessions, if the job recalled is different than the job given at PRE, remind the subject of the original job and date provided, and proceed with questions 1-5.

QUESTION 1: WHAT WAS YOUR TITLE WHEN LAST WORKING AT THIS JOB?

3 MOS POST: job title	score	6 MOS POST: job title	score	12 MOS POST: job title	score

QUESTION 2: WHAT WAS THE FIRST AND LAST NAME OF YOUR SUPERVISOR?

3 MO POST: supervisor's name	score	6 MO POST: supervisor's name	score	12 MO POST: supervisor's name	score

QUESTION 3: WHAT WAS THE COMPLETE ADDRESS OF THE BUILDING WHERE YOU WO

3 MOS POST: address	score	6 MOS POST: address	score	12 MOS POST: address	score
number & street:		number & street:		number & street:	
city: state:		city: state:		city: state:	
zip code:		zip code:		zip code:	

QUESTION 4: WHAT WAS YOUR PHONE NUMBER WITH AREA CODE AT THIS JOB?

3 MOS POST: phone number	score	6 MOS POST: phone number	score	12 MOS POST: phone number	score

QUESTION 5: IN WHAT MONTH AND YEAR DID YOU FIRST START WORKING FOR THIS EMPL

3 MO POST: mo & yr job began	score	6 MO POST: mo & yr job began	score	12 MO POST: mo & yr job began	score

3 MOS POST: total score	6 MOS POST: total score	12 MOS POST: total score

PART 6: PHYSICAL

(11)

Interviewer: You will begin this section by asking the subject to recall the MOST RECENT physical illness for which he/she consulted a physician, before entering the program. If the subject's most recent doctor's visit was for a check-up, ask him/her to recall the most recent visit that involved a physical complaint.

I AM GOING TO ASK YOU SOME QUESTIONS ABOUT THE LAST TIME YOU CONSULTED A PHYS FOR A PHYSICAL COMPLAINT OR ILLNESS BEFORE YOU ENTERED THIS PROGRAM. WHY DID YO GO TO SEE A DOCTOR; WHAT WERE YOUR COMPLAINTS?

NOTES:

PRE: complaint	POST: complaint

NOTES:

IN WHAT MONTH AND YEAR DID THIS CONSULTATION TAKE PLA

NOTES:

PRE: month & year of visit

Interviewer: At POST, if the illness recalled is different than the one given at PRE, remind the subject of the original illness and date, and proceed with questions 1-5.

QUESTION 1: WHAT WAS THE FIRST AND LAST NAME OF THE DOCTOR WHOM YOU SAW AT THI

NOTES:

PRE: Dr.'s name	score	POST: Dr.'s name	score

QUESTION 2: WHAT WAS THE NAME AND ADDRESS OF THE BUILDING OR HOSPITAL WHERE Y(YOUR DOCTOR?

NOTES:

PRE: Dr.'s address	score	POST: Dr.'s address	score
name of building or hospital:		name of building or hospital:	
number & street:		number & street:	
city: state:		city: state:	
zip code:		zip code:	

QUESTION 3: ON WHAT FLOOR OF THIS BUILDING OR HOSPITAL WAS YOUR APPOINTI

NOTES:

PRE: floor	score	POST: floor	score

QUESTION 4: WHAT TREATMENTS OR MEDICATIONS WERE PRESCRIBED FOR YOU?

NOTES:

PRE: treatment	score	POST: treatment	score

QUESTION 5: IN WHAT MONTH AND YEAR DID YOU FIRST NOTICE YOUR SYMPT

NOTES:

PRE: mo & yr symps	score	POST: mo & yr symps	score

PRE: total score	POST: total score

PART 6: PHYSICAL (12)

Interviewer: You will begin this section by asking the subject to recall the MOST RECENT physical illness for which he/she consulted a physician before entering the program. If the subject's most recent doctor's visit was for a check-up, ask him/her to recall the most recent visit that involved a physical complaint.

I AM GOING TO ASK YOU SOME QUESTIONS ABOUT THE LAST TIME YOU CONSULTED A PHYSI FOR A PHYSICAL COMPLAINT OR ILLNESS BEFORE YOU ENTERED THIS PROGRAM. WHY DID GO TO SEE A DOCTOR; WHAT WERE YOUR COMPLAINTS?

3MOS POST: complaint	6MOS POST: complaint	12MOS POST: complaint
NOTES:	NOTES:	NOTES:

Interviewer: At all POST testing sessions, if the illness recalled is different than the one given at PRE, remind the subject of the original illness and date, and proceed with questions 1-5.

QUESTION 1: WHAT WAS THE FIRST AND LAST NAME OF THE DOCTOR WHOM YOU SAW AT THI

3MOS POST: Dr.'s name	score	6MOS POST: Dr.'s name	score	12MOS POST: Dr.'s name	score

QUESTION 2: WHAT WAS THE NAME AND ADDRESS OF THE BUILDING OR HOSPITAL WHERE Y(YOUR DOCTOR?

3MOS POST: Dr.'s address	score	6MOS POST: Dr.'s address	score	12MOS POST: Dr.'s address	score
name of building or hospital:		name of building or hospital:		name of building or hospital:	
number & street:		number & street:		number & street:	
city: state:		city: state:		city: state:	
zip code:		zip code:		zip code:	

QUESTION 3: ON WHAT FLOOR OF THIS BUILDING OR HOSPITAL WAS YOUR APPOINTI

3MOS POST: floor	score	6MOS POST: floor	score	12MOS POST: floor	score

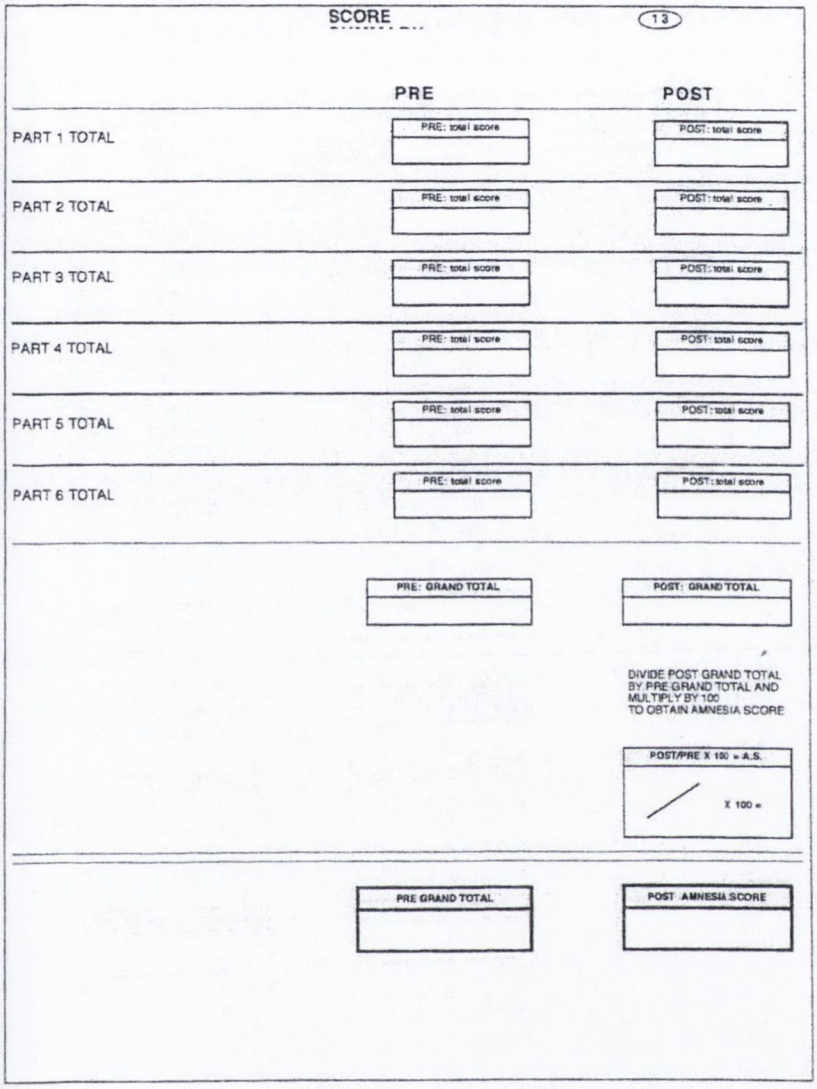
QUESTION 4: WHAT TREATMENTS OR MEDICATIONS WERE PRESCRIBED FOR YOU?

3MOS POST: treatment	score	6MOS POST: treatment	score	12MOS POST: treatment	score

QUESTION 5: IN WHAT MONTH AND YEAR DID YOU FIRST NOTICE YOUR SYMPT

3MOS POST: mo & yr symps	score	6MOS POST: mo & yr symps	score	12MOS POST: mo & yr symps	score

3 MOS POST: total score	6 MOS POST: total score	12 MOS POST: total score


SCORE
13
PRE
POST
PART 1 TOTAL
PRE: total score
POST: total score
PART 2 TOTAL
PRE: total score
POST: total score
PART 3 TOTAL
PRE: total score
POST: total score
PART 4 TOTAL
PRE: total score
POST: total score
PART 5 TOTAL
PRE: total score
POST: total score
PART 6 TOTAL
PRE: total score
POST: total score
PRE: GRAND TOTAL
POST: GRAND TOTAL
DIVIDE POST GRAND TOTAL BY PRE GRAND TOTAL AND MULTIPLY BY 100 TO OBTAIN AMNESIA SCORE
POST/PRE X 100 = A.S.
X 100 =
PRE GRAND TOTAL
POST: AMNESIA SCORE

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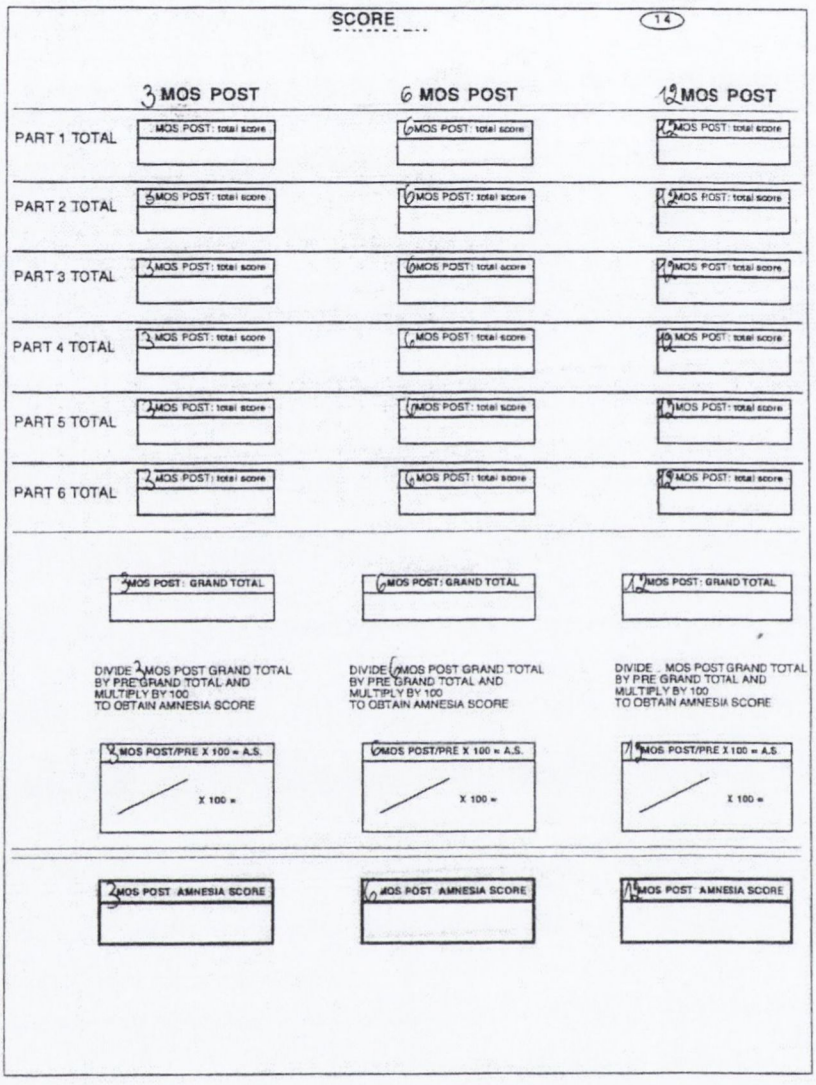
SCORE
14
3 MOS POST
6 MOS POST
12 MOS POST
PART 1 TOTAL
PART 2 TOTAL
PART 3 TOTAL
PART 4 TOTAL
PART 5 TOTAL
PART 6 TOTAL
MOS POST: total score
MOS POST: GRAND TOTAL
DIVIDE MOS POST GRAND TOTAL BY PRE GRAND TOTAL AND MULTIPLY BY 100 TO OBTAIN AMNESIA SCORE
MOS POST/PRE X 100 = A.S.
X 100 =
MOS POST AMNESIA SCORE

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APPENDIX 11: EVENTS QUESTIONNAIRES

Version 1

	1991-1995	1996-2000	2001-2006
1. Which city in Louisiana, USA was severely affected by Hurricane Katrina in 2005? **New Orleans**, Baton Rouge, Detroit, New Haven			□
2. Which former US vice president won the 2007 Nobel Peace Prize for his work on climate change? Dan Quayle, Dick Cheney, **Al Gore**, Richard Perle			
3. Which British Actor, known for his roles in the Star Wars films and the Ladykillers, died in 2000? Peter Sellers, **Alec Guinness**, Peter O'Toole, John Hurt		□	
4. Which Fianna Fáil leader was elected Taoiseach in January 1993? **Albert Reynolds**, Garret Fitzgerald, Bertie Ahern, Charles Haughey	□		
5. Which former president of Serbia was found dead in his cell in The Hague in 2006? Radovan Karidic, General Tito, **Slobodan Milosevic**, Ratko Mladic		□	□
6. What was the name of the Russian Submarine that sank in 2000 in the Berints Sea with the loss of all crew? The October, The Pyotr Velikiy, The Komsomolets, **The Kursk**	□		
7. In which country were the FIFA world cup soccer finals held in 1994? England, Canada, **USA**, Germany			□
8. Which famous Irish singer died on the 26th of December 2007? Dana, **Joe Dolan**, Paddy Reilly, Luke Kelly			□
9. Which Italian side won the UEFA champions league title in 2007 after beating Liverpool 2-1? **AC Milan**, Inter Milan, Juventus, Roma	□		□
10. Which now famous Dublin structure was completed in 2003? Nelson's Column, **The (Millenium) Spire (of Dublin)**, Croke Park, Landsdowne Road		□	
11. What was the name of the first novel written by Cecelia Ahern daughter of An Taoiseach Bertie Ahern? **PS I Love You**, The Sea, The God of Small Things, Our Fathers		□	
12. Who did Enda Kenny replace as leader of Fine Gael in 2002? John Bruton, Jim Mitchell, **Michael Noonan**, Garrett Fitgerald			
13. In 1995, Which Bosnian town was the site of a massacre of men and boys during the Yugoslav war? Mostar, Belgrade, Krajina, **Srebernica**			
14. Who played the lead character in the film "Gladiator"? Brad Pitt, Denzel Washington, Harrison Ford, **Russell Crowe**			
15. Who became the United Nations Secretary-General of the on the 1st of January 2007? Butros Butros-Gali, **Ban Ki-moon,** Kofi Annan, Mary Robinson			
16. In which country were the FIFA world cup soccer finals held in 1998? England, Germany, **France,** Holland			

	1991-1995	1996-2000	2001-2006
17. What was the name of the Irish Crime Reporter who was shot dead in Dublin in 1996? Emily O'Reilly, **Veronica Guerin**, Yvonne Fletcher, Veronica Lake			
18. Which former American Football star was arrested for the murder of his ex-wife Nicole and her friend Ron Goldman? **OJ Simpson**, Joe Montana, Bruce Smyth, Bill Giles		☐	
19. In which African Country did rioting take place after general elections in late 2007? Somalia, Botswana, **Kenya**, South Africa		☐	
20. Which former US president died in 1994 in New York City? Gerald Ford, Harry Truman, Ronald Reagan, **Richard Nixon**			
21. Which Irish Author won the 2007 Man Booker Prize for the novel "The Gathering"? Ann Wilson, **Anne Enright**, Séamus Heaney, Dermot Bolger	☐		
22. Which former manager and player was removed from the Ireland soccer team in 2007? Brian Kerr, Jack Charlton, **Steve Staunton**, Niall Quinn			
23. In 2003, 100,000 people took to the streets of Dublin and Belfast to protest against the imminent invasion of which country? Afghanistan, Iran, Syria, **Iraq**		☐	
24. Which former Actor was elected as governor of California in 2003? Ronald Reagan, Harrison Ford, **Arnold Schwarzenegger**, Ted Dansen			☐
25. Who hosted the Late Late Show on RTE up until 1999? Pat Kenny, Ray Darcy, Darragh O`Brian, **Gay Byrne**			☐
26. Name the princess who was killed following a high speed car accident in a road tunnel in Paris? Anne, **Diana**, Margaret, Elizabeth		☐	
27. In which country were the FIFA world cup soccer finals held in 2006? England, France, **Germany**, Holland	☐		
28. Which former US President won the 2002 Nobel Peace Prize for his diplomatic work in international conflicts? **Jimmy Carter**, Ronald Reagan, George Bush, Richard Nixon			
29. In 1998, a bomb placed by the real IRA exploded on a Saturday morning in which town? Newry, **Omagh**, Enniskillen, Portadown			
30. Name the 5 member girl band that had hits like "Wannabe" and "Who do you think you are?" Girls Aloud, Sugarbabes, **Spice Girls**, All Saints			
31. Which coach led Ireland to the quarter finals of the 1994 soccer World Cup? Brian Kerr, Mick Mc Carthy, **Jack Charlton**, Steve Staunton			
	1991-1995	1996-2000	2001-2006

32. Who was promoted to chief executive of low-cost airline Ryanair in 1994?
David O'Leary, **Michael O'Leary**, Dermot Mannion, Willie Walsh

33. In 2000, who became the first golfer to win 3 Majors in a calendar year since Ben Hogan in 1953?
Padraig Harrington, Nick Faldo, Vijay Singh, **Tiger Woods**

34. Which famous Italian Tenor died on September 6th 2007?
Placido Domingo, **Luciano Pavarotti**, José Carreras, Maria Callas

35. Who created "Lord of the Dance", the Irish Musical and Dance production in 1996?
Michael Flately, Colin Dunne, Jean Butler, Conor Smith

36. In 2007, which party entered coalition government with Fianna Fáil for the first time?
The Progressive Democrats, The Labour Party, **The Green Party**, The Worker's Party

37. Which famous female tennis player was stabbed on court in 1993?
Martina Hingis, **Monica Seles**, Martina Navratilova, Jennifer Capriati

38. Which Irish singer had a world wide hit with the song "Nothing Compares to You"?
Sinead O`Connor, Kate Bush, Mary Black, Eleanor Mc Evoy

39. Who became the President of the French Republic on May 16th 2007?
Jacques Chirac, Francois Mitterand, Lionel Jospin, **Nicolas Sarkozy**

40. Which boxer took the first gold medal for an Irish athlete in the Barcelona Olympics?
Michael Carruth, Frank Bruno, Wayne McCullagh, Mike Tyson

41. Which two South African politicians won the Nobel Peace prize in 1993 for working towards Democracy and an end to Apartheid?
Steve Biko & Nelson Mandela. **Nelson Mandela & FW De Clerk**, Nelson Mandela & Winnie Mandela, Steve Biko & Winnie Mandela

42. Which 2003 NASA Space shuttle disintegrated on re-entry killing all crew?
Endeavour, **Columbia**, Atlantis, Discovery

43. Which team beat Galway to win the All Ireland Senior Hurling Championship in 2005?
Cork, Kilkenny, Tipperary , Limerick

44. Which English player was sent off in the 1998 World Cup Football quarter finals against Argentina?
Alan Shearer, Michael Owen, Stuart Pearce, **David Beckham**

45. Which former Pakistani Prime Minister was assassinated on December 27th 2007?
Nawaz Sharif, **Benazir Bhutto**, Indira Gandhi, Tarviz Musharaf

46. Name the actor who won the Oscar for "Forrest Gump"?
Harrison Ford, Jack Nicholson, **Tom Hanks**, Robert de Niro

	1991-1995	1996-2000	2001-2006
47. What was the name of the controversial Irish swimmer who won 3 gold medals in the 1996 Olympics? Natalie Coughlin, **Michelle Smith**, Jenny Thompson, Lynn Joyce		□	
48. Who was the English journalist held as a hostage in Lebanon, who was released in late 1991? **John McCarthy**, Terry Waite, Brian Keenan, Jackie Mann	□	□	
49. Which two Northern Irish politicians won the Nobel Peace Prize in 1997 for their work in the Peace Process? Ian Paisley & Gerry Adams, John Hume & Ian Paisley, **John Hume & David Trimble**, David Trimble & Ian Paisley			□
50. Which natural disaster took place in South East Asia on the 26th of December 2004? Volcanic Eruption, Hurricane, Landslide, **Tsunami**			□
51. Who was sworn in as President of Afghanistan in 2001? Ruhollah Khomeini, Saddam Hussein, **Hamid Karzai,** Ahmed Shah Massoud		□	
52. What was the name of the young British girl abducted on holidays in Portugal in 2007? **Madeleine McCann**, Kate McCann, Alison McCann, Alison McGrath	□		□
53. Which country won the 2003 Rugby World Cup? Australia, New Zealand, France, **England**			
54. What was the name of the white house aide with whom President Bill Clinton was accused of having an affair? Louise Farrell, **Monica Lewinsky**, Paula Jones, Susan Macmillan	□		□
55. What was the name of the lead singer of "Queen" who died of HIV related illness? Peter Allen, Paul Jacobs, **Freddie Mercury**, Steven Grossman			
56. Who took over from Tony Blair as leader of the Labour Party and Prime minister of the United Kingdom in 2007? **Gordon Brown**, Robin Cook, David Blunkett, Peter Haine			
57. Which Swiss tennis player in 2004 won 3 of the 4 Grand Slam men's singles tournament? Andy Rodic, Leyton Hewitt, **Roger Federer**, Marat Safin			
58. Which actor in 1995 was seriously injured during a riding accident and left wheelchair – bound? Billy Crystal, **Christopher Reeve**, Adam Sandler, Alan Watts			
59. Which former president of the USA was buried on January 3rd 2007? Ronald Reagan, Jimmy Carter, **Gerald Ford**, Richard Nixon			
60. What was the name of the film adaptation of a Cormac MacCarthy Novel that Won Best Film at the 80th Academy Awards in 2008? **No Country for Old men**, Atonement, Sweeney Todd, The diving bell and the butterfly			

Version 2	1993-1997	1998-2002	2003-2007	2008
1) Which two South African politicians won the Nobel Peace prize in 1993 for working towards Democracy and an end to Apartheid? Steve Biko & Nelson Mandela. **Nelson Mandela & FW De Clerk**, Nelson Mandela & Winnie Mandela, Steve Biko & Winnie Mandela	☐			
2) What was the name of the treaty which was rejected in Ireland in June 2008? **The Lisbon Treaty**, The Nice Treaty, The Maastricht Treaty, The Madrid Treaty				☐
3) In 1998, a bomb placed by the Real IRA exploded on a Saturday morning in which town? Newry, **Omagh**, Enniskillen, Portadown		☐		
4) What was the name of a film adaptation of a Cormac McCarthy novel that won Best Film at the 80th Academy awards in 2008? **No Country for Old men,** Atonement, Sweeney Todd, The Diving Bell and the Butterfly				☐
5) Which former Taoiseach who was originally from County Cork died in October 1999? Charlie Haughey, Seán Lemass, Liam Cosgrave, **Jack Lynch**		☐		
6) What was the name of the controversial Irish swimmer who won 3 gold medals in the 1996 Olympics? Natalie Coughlin, **Michelle Smith**, Jenny Thompson, Lynn Joyce	☐			
7) Which British actress starred in the film "Titanic" in 1997? Kate Beckinsale, Keira Knightley, **Kate Winslet,** Helen Mirren	☐			
8) Senior citizens marched in protest in Dublin in November 2008 after the removal of what benefit in the Budget? Free travel, Fuel allowance, Childrens allowance, **Medical cards**				☐
9) Which famous Irish singer from Mullingar died on the 26th of December 2007? Dana, **Joe Dolan**, Paddy Reilly, Luke Kelly			☐	

	1993-1997	1998-2002	2003-2007	2008
10) Which Irish golfer won the British Open Championship and the USPGA tour in 2008? Darren Clarke, **Padraig Harrington,** Paul McGinley, Christy O'Connor				☐
11) Which country both hosted and won the World Cup Soccer finals in 1998? England, Germany, **France,** Holland		☐		
12) Which city in Louisiana, USA, was severely affected by Hurricane Katrina in 2005? **New Orleans**, Baton Rouge, Detroit, New Haven			☐	
13) Name the princess who was killed following a high speed car accident in a road tunnel in Paris? Anne, **Diana**, Margaret, Elizabeth	☐			
14) Which famous female tennis player was stabbed on court in 1993? Martina Hingis, **Monica Seles**, Martina Navratilova, Jennifer Capriati	☐			
15) Which now famous Dublin structure, on O'Connell Street was completed in 2003? Nelson's Column, **The (Millenium) Spire (of Dublin)**, Croke Park, Landsdowne Road			☐	
16) Which Irish politician was appointed UN High Commissioner for Human Rights in 1997? **Mary Robinson,** Mary McAleese, Adi Roche, Mary Harney	☐			
17) Which Fianna Fáil TD was sentenced to 6 months imprisonment for tax offences as a result of legislation he had passed? Bertie Ahern, Charlie Haughey, **Ray Burke,** Tony O'Reilly			☐	
18) Which former president of Serbia was found dead in his cell in The Hague in 2006? Radovan Karidic, General Tito, **Slobodan Milosevic**, Ratko Mladic			☐	
19) What was the name of the world's first successfully cloned mammal? Percy the pig, Harry the horse, **Dolly the sheep,** Daisy the cow	☐			

	1993-1997	1998-2002	2003-2007	2008
20) What was the name of the Alaskan politician who ran for vice-president in the 2008 American presidential elections? **Sarah Palin**, Condoleeza Rice, John Kerry, John McCain				☐
21) Name the Cambodian Khmer Rouge leader who died in 1998, whose attempts to form a Communist society resulted in the deaths of 25 percent of the country's population? Ho Chi Minh, General Mao, **Pol Pot,** Idi Amin		☐		
22) On November 24, 1995, the Irish population voted to remove Ireland's constitutional ban on what issue? Abortion, Smoking, **Divorce,** Euthanasia	☐			
23) Who was the British journalist and presenter of the BBC program *Crimewatch* who was shot dead on the doorstep of her home in April 1999? **Jill Dando,** Anne Diamond, Fiona Bruce, Kay Burley		☐		
24) What was the name of the Russian Submarine that sank in 2000 in the Berints Sea with the loss of all its crew? The October, The Pyotr Velikiy, The Komsomolets, **The Kursk**		☐		
25) Who was promoted to chief executive of low-cost airline Ryanair in 1994? David O'Leary, **Michael O'Leary**, Dermot Mannion, Willie Walsh	☐			
26) Which Indian city was the site of terrorist attacks on tourists in November 2008? Delhi, Calcutta, **Mumbai,** Goa				☐
27) Who hosted the Late Late Show on RTE up until 1999? Pat Kenny, Ray Darcy, Dara O`Brian, **Gay Byrne**		☐		
28) What was the name of the Irish Crime Reporter who was shot dead in Dublin in 1996? Emily O'Reilly, **Veronica Guerin**, Yvonne Fletcher, Veronica Lake	☐			
29) Who was the American swimmer who won 8 gold medals in the 2008 Olympic games? Ian Thorpe, Mark Spitz, **Michael Phelps,** Barry Murphy				☐

	1993-1997	1998-2002	2003-2007	2008
30) Who did Enda Kenny replace as leader of Fine Gael in 2002? John Bruton, Jim Mitchell, **Michael Noonan**, Garrett Fitgerald		☐		
31) Which American figure skater was attacked by fellow skater Tonya Harding's ex-husband prior to the 1994 Winter Olympics, in a bid to remove her from the American Olympic team? Jane Torville, **Nancy Kerrigan,** Sarah Coen, Michelle Kwan	☐			
32) Who played the lead character in the film "Gladiator"? Brad Pitt, Denzel Washington, Harrison Ford, **Russell Crowe**		☐		
33) Which region in the former Yugoslavia declared itself a republic in early 2008? Bosnia, Slovenia, Croatia, **Kosovo**				☐
34) Which Irish politician resigned in May 2008 after being Taoiseach for 11 years? Brian Cowen, Mary Harney, Albert Reynolds, **Bertie Ahern**				☐
35) Which Fianna Fáil leader was elected Taoiseach in January 1993? **Albert Reynolds**, Garret Fitzgerald, Bertie Ahern, Charles Haughey	☐			
36) What nationwide ban came into effect in public places in March 2004? Hunting ban, **Smoking ban,** shooting ban, drinking ban			☐	
37) Which county won the all Ireland football final in 2008? Kerry, Cork, **Tyrone,** Armagh				☐
38) Which former actor was elected as Governor of California in 2003? Ronald Reagan, Harrison Ford, **Arnold Schwarzenegger**, Ted Dansen			☐	
39) Which soccer player left the Irish squad in the middle of the 2002 World Cup after a row with the manager in Saipan? Niall Quinn, Robbie Keane, Stephen Ireland, **Roy Keane**		☐		
40) Which former American Football star was arrested for the murder of his ex-wife Nicole and her friend Ron Goldman? **OJ Simpson**, Joe Montana, Bruce Smyth, Bill Giles	☐			
41) Which animals were at the centre of a food contamination scare in Ireland in late 2008? Lambs, **pigs,** cattle, poultry				☐

	1993-1997	1998-2002	2003-2007	2008
42) Which team beat Galway to win the All Ireland Senior Hurling Championship in 2005? **Cork**, Kilkenny, Tipperary , Limerick			☐	
43) What was the name of the first novel written by Cecelia Ahern daughter of former Taoiseach Bertie Ahern? **PS I Love You**, The Sea, The God of Small Things, Our Fathers			☐	
44) Which natural disaster took place in South East Asia on the 26th of December 2004? Volcanic Eruption, Hurricane, Landslide, **Tsunami**			☐	
45) Which former US President won the 2002 Nobel Peace Prize for his diplomatic work in international conflicts? **Jimmy Carter**, Ronald Reagan, George Bush, Richard Nixon		☐		
46) What animal disease outbreak in 2001 caused the closure of public parks and gardens, the cancellation of the St. Patrick's day parade and the culling of thousands of animals in Ireland and the UK? Bird Flu, Bluetongue, **Foot and mouth,** Mad cow disease		☐		
47) In a controversial decision Aer Lingus decided to cease direct flights between Heathrow airport and which Irish airport in 2008? **Shannon,** Knock, Cork, Galway				☐
48) Which controversial former Taoiseach, know for his extravagant lifestyle died in 2006? **Charlie Haughey,** Albert Reynolds, John Bruton, Garret Fitzgerald			☐	
49) Which late actor played "the Joker" in the 2008 Batman film "The Dark Knight"? Christian Bale, Jack Nicholson, Jim Carey, **Heath Ledger**				☐
50) In 1995, Which Bosnian town was the site of a massacre of men and boys during the Yugoslav war? Mostar, Belgrade, Krajina, **Srebernica**	☐			
51) In which country were the FIFA World Cup soccer finals held in 2006? England, France, **Germany**, Holland			☐	
52) Who resigned as President of Cuba in February 2008? General Pinochet, Juan Peron, Che Guevara, **Fidel Castro**				☐

	1993-1997	1998-2002	2003-2007	2008
53) In 2003, which country was invaded by British, American, Australian and Polish troops amid fears of it harbouring weapons of mass destruction? Afghanistan, Iran, Syria, **Iraq**			☐	
54) What was the name of the criminal who was extradited from the UK back to Ireland on drug trafficking charges and the suspected murder of Veronica Guerin? **John Gilligan,** Martin Cahill, Gerry Hutch, Paul Ward		☐		
55) Which party entered coalition government with Fianna Fail for the first time in 2007? The Progressive democrats, The Labour Party, **The Green Party,** the Workers Party			☐	
56) Which actor in 1995 was seriously injured during a riding accident and left wheelchair – bound? Billy Crystal, **Christopher Reeve**, Adam Sandler, Alan Watts	☐			
57) Which member of the Beatles died in 2001 aged 58? Paul McCartney, **George Harrison,** John Lennon, Ringo Starr		☐		
58) Which former Pakistani Prime Minister was assassinated on December 27th 2007? Nawaz Sharif, **Benazir Bhutto**, Indira Gandhi, Tarviz Musharaf			☐	
59) Who was sworn in as President of Afghanistan in 2001? Ruhollah Khomeini, Saddam Hussein, **Hamid Karzai,** Ahmed Shah Massoud		☐		
60) Which south-east Asian country was devastated by cyclone Nargis in early 2008? Thailand, Vietnam, **Burma,** Malaysia				☐

VERSION 3	Jul93-Jun98	Jul98-Jun03	Jul03-Jun08	Jul08-Jun 09
1) Name the Cambodian Khmer Rouge leader who died in 1998, whose attempts to form a Communist society resulted in the deaths of 25 percent of the country's population? Ho Chi Minh, General Mao, **Pol Pot,** Idi Amin		☐		
2) Who was the British journalist and presenter of the BBC program *Crimewatch* who was shot dead on the doorstep of her home in April 1999? **Jill Dando,** Anne Diamond, Fiona Bruce, Kay Burley		☐		
3) What was the name of the controversial Irish swimmer who won 3 gold medals in the 1996 Olympics? Natalie Coughlin, **Michelle Smith**, Jenny Thompson, Lynn Joyce	☐			
4) Which two South African politicians won the Nobel Peace prize in 1993 for working towards Democracy and an end to Apartheid? Steve Biko & Nelson Mandela. **Nelson Mandela & FW De Clerk**, Nelson Mandela & Winnie Mandela, Steve Biko & Winnie Mandela	☐			
5) Senior citizens marched in protest in Dublin in November 2008 after the removal of what benefit in the budget? Free travel, Fuel allowance, Childrens allowance, **Medical cards**				☐
6) Which animals were at the centre of a food contamination scare in Ireland in late 2008? Lambs, **pigs,** cattle, poultry				☐
7) Which member of the Beatles died in 2001 aged 58? Paul McCartney, **George Harrison,** John Lennon, Ringo Starr		☐		
8) Which Irish politician was appointed UN High Commissioner for human rights in 1997? **Mary Robinson,** Mary McAleese, Adi Roche, Mary Harney	☐			
9) Which Irish golfer won the British Open championship and the USPGA tour in 2008? Darren Clarke, **Padraig Harrington,** Paul McGinley, Christy O'Connor				☐

	Jul93-Jun98	Jul98-Jun03	Jul03-Jun08	Jul08-Jun 09
10) Who did Enda Kenny replace as leader of Fine Gael in 2002? John Bruton, Jim Mitchell, **Michael Noonan**, Garrett Fitgerald		☐		
11) Which now famous Dublin structure on O'Connell Street was completed in 2003? Nelson's Column, **The (Millenium) Spire (of Dublin)**, Croke Park, Landsdowne Road		☐		
12) In which country were the FIFA world cup soccer finals held in 2006? England, France, **Germany**, Holland			☐	
13) Who was sworn in as President of Afghanistan in 2001? Ruhollah Khomeini, Saddam Hussein, **Hamid Karzai,** Ahmed Shah Massoud		☐		
14) What nationwide ban came into effect in public places in March 2004? Hunting ban, **Smoking ban,** shooting ban, drinking ban			☐	
15) Which Indian city was the site of terrorist attacks on tourists in November 2008? Delhi, Calcutta, **Mumbai,** Goa				☐
16) What was the name of the Alaskan politician who ran for vice-president in the 2008 American presidential elections? **Sarah Palin**, Condoleeza Rice, John Kerry, John McCain				☐
17) Which controversial former Taoiseach, known for his extravagant lifestyle, died in 2006? **Charlie Haughey,** Albert Reynolds, John Bruton, Garret Fitzgerald			☐	
18) In a controversial decision Aer Lingus decided to cease direct flights between Heathrow airport and which Irish airport in 2008? **Shannon,** Knock, Cork, Galway				☐
19) What was the name of the Treaty that was rejected in Ireland in June 2008? **The Lisbon Treaty**, The Nice Treaty, The Maastricht Treaty, The Madrid Treaty			☐	

	Jul93-Jun98	Jul98-Jun03	Jul03-Jun08	Jul08-Jun 09
20) Which former Taoiseach, originally from County Cork, died in October 1999? Charlie Haughey, Seán Lemass, Liam Cosgrave, **Jack Lynch**		☐		
21) Who became 44th President of the United States on January 20th 2009? Joe Biden, John McCain, Hilary Clinton, **Barack Obama**				☐
22) Which American swimmer won 8 gold medals in the 2008 Olympic games? Ian Thorpe, Mark Spitz, **Michael Phelps,** Barry Murphy				☐
23) Which actor in 1995 was seriously injured during a riding accident and left wheelchair – bound? Billy Crystal, **Christopher Reeve**, Adam Sandler, Alan Watts	☐			
24) What was the name of the world's first successfully cloned mammal? Percy the pig, Harry the horse, **Dolly the sheep,** Daisy the cow	☐			
25) Which county won the all Ireland football final in 2008? Kerry, Cork, **Tyrone,** Armagh				☐
26) In 1995, which Bosnian town was the site of a massacre of men and boys during the Yugoslav war? Mostar, Belgrade, Krajina, **Srebernica**	☐			
27) What animal disease outbreak in 2001 caused the closure of public parks and gardens, the cancellation of the St. Patrick's day parade and the culling of thousands of animals in Ireland and the UK? Bird Flu, Bluetongue, **Foot and mouth,** Mad cow disease		☐		
28) Which Irish actor won a Golden Globe in January 2009 for his performance in the film "In Bruges"? Gabriel Byrne, Liam Neeson, **Colin Farrell,** Daniel Day-Lewis				☐
29) Which natural disaster took place in South East Asia on the 26th of December 2004? Volcanic Eruption, Hurricane, Landslide, **Tsunami**			☐	

	Jul93-Jun98	Jul98-Jun03	Jul03-Jun08	Jul08-Jun 09
30) Which world famous American popstar, famous for hits like "Thriller" and "Billy-Jean" died in June 2009? Frank Sinatra, Justin Timberlake, **Michael Jackson,** Bruce Springsteen				☐
31) Which city in Louisiana, USA was severely affected by Hurricane Katrina in 2005? **New Orleans**, Baton Rouge, Detroit, New Haven			☐	
32) Which former actor was elected as governor of California in 2003? Ronald Reagan, Harrison Ford, **Arnold Schwarzenegger**, Ted Dansen			☐	
33) On November 24, 1995, the Irish population voted to remove Ireland's constitutional ban on what issue? Abortion, Smoking, **Divorce,** Euthanasia	☐			
34) Which British actress starred in the film "Titanic" in 1997? Kate Beckinsale, Keira Knightley, **Kate Winslet,** Helen Mirren	☐			
35) Which famous female tennis player was stabbed on court in 1993? Martina Hingis, **Monica Seles**, Martina Navratilova, Jennifer Capriati	☐			
36) Which famous Irish singer from Mullingar died on the 26th of December 2007? Dana, **Joe Dolan**, Paddy Reilly, Luke Kelly			☐	
37) Which American figure skater was attacked by fellow skater Tonya Harding's ex-husband prior to the 1994 Winter Olympics, in a bid to remove her from the American Olympic team? Jane Torville, **Nancy Kerrigan,** Sarah Coen, Michelle Kwan	☐			
38) Which party entered coalition government with Fianna Fail for the first time in 2007? The Progressive democrats, The Labour Party, **The Green Party,** the Workers Party			☐	
39) Which former president of Serbia was found dead in his cell in The Hague in 2006? Radovan Karidic, General Tito, **Slobodan Milosevic**, Ratko Mladic			☐	

	Jul93-Jun98	Jul98-Jun03	Jul03-Jun08	Jul08-Jun 09
40) Which team beat Galway to win the All Ireland Senior Hurling Championship in 2005? **Cork**, Kilkenny, Tipperary , Limerick			☐	
41) What was the name of the Russian Submarine that sank in 2000 in the Berints Sea with the loss of all crew? The October, The Pyotr Velikiy, The Komsomolets, **The Kursk**		☐		
42) What new influenza virus spread from Mexico throughout the world in April 2009? **Swine flu,** Avian flu, Spanish flu, Hawaiian flu				☐
43) Which Asian country came under international scrutiny in May 2009 after carrying out tests of nuclear weapons? South Korea, China, **North Korea,** Japan				☐
44) Which former Pakistani Prime Minister was assassinated on December 27th 2007? Nawaz Sharif, **Benazir Bhutto**, Indira Gandhi, Tarviz Musharaf			☐	
45) Which Fianna fáil TD was sentenced to 6 months imprisonment for tax offences in 2005 as a result of legislation he had passed? Bertie Ahern, Charlie Haughey, **Ray Burke,** Tony O'Reilly			☐	
46) What was the name of the Irish Crime Reporter who was shot dead in Dublin in 1996? Emily O'Reilly, **Veronica Guerin**, Yvonne Fletcher, Veronica Lake	☐			
47) Which former American Football star was arrested in 1994 for the murder of his ex-wife Nicole and her friend Ron Goldman? **OJ Simpson**, Joe Montana, Bruce Smyth, Bill Giles	☐			
48) Who was promoted to chief executive of low-cost airline Ryanair in 1994? David O'Leary, **Michael O'Leary**, Dermot Mannion, Willie Walsh	☐			
49) Who hosted the Late Late Show on RTE up until 1999? Pat Kenny, Ray Darcy, Darragh O`Brian, **Gay Byrne**		☐		
50) Which country both hosted and won the FIFA world cup soccer finals in 1998? England, Germany, **France,** Holland		☐		

	Jul93-Jun98	Jul98-Jun03	Jul03-Jun08	Jul08-Jun 09
51) Which former US President won the 2002 Nobel Peace Prize for his diplomatic work in international conflicts? **Jimmy Carter**, Ronald Reagan, George Bush, Richard Nixon		☐		
52) In 1998, a bomb placed by the Real IRA exploded on a Saturday morning in which town? Newry, **Omagh**, Enniskillen, Portadown	☐			
53) What was the name of the first novel written by Cecelia Ahern daughter of An Taoiseach Bertie Ahern? **PS I Love You**, The Sea, The God of Small Things, Our Fathers			☐	
54) What type of structure, named after Samuel Beckett, was delivered from Holland to Dublin in May 2009? A roof, a belltower, a statue, **a bridge**				☐
55) Who played the lead character in the film "Gladiator"? Brad Pitt, Denzel Washington, Harrison Ford, **Russell Crowe**		☐		
56) In 2003, which country was invaded by British, American, Australian and Polish troops amid fears of it harbouring weapons of mass destruction? Afghanistan, Iran, Syria, **Iraq**			☐	
57) Which soccer player left the Irish squad in the middle of the 2002 World Cup after a row with the manager in Saipan? Niall Quinn, Robbie Keane, Stephen Ireland, **Roy Keane**		☐		
58) What was the name of the criminal who was extradited from the UK back to Ireland on drug trafficking charges and the suspected murder of Veronica Guerin? **John Gilligan,** Martin Cahill, Gerry Hutch, Paul Ward		☐		
59) Which Irish news reporter left RTE to become a candidate for Fine Gael in the Dublin South by-election in May 2009? Brian Dobson, **George Lee,** Charlie Bird, George Hook				☐
60) Name the princess who was killed in 1997 following a high speed car accident in a road tunnel in Paris? Anne, **Diana**, Margaret, Elizabeth	☐			

Name:
Date:

BUSCHKE 16 (Version 1)

Semantic category	Target	Imm.R.	F.R.1	C.R. 1	F.R. 2	C.R. 2	F.R.3	C.R.3	D.F.R.	D.C.R.
Fish	Herring									
Clothing	Pyjamas									
Toy	Dice									
Flower	Lily									
Utensil	Knife									
Fruit	Grapes									
Animal	Fox									
Musical instrument	Drums									
Bird	Dove									
Vegetable	Celery									
Body part	Stomach									
Profession	Dentist									
Vehicle	Train									
Tool	Axe									
Tree	Birch									
Piece of furniture	Sideboard									
TOTAL										

TOTAL F.R. + C.R. [ ] [ ] [ ] [ ]

Imm. R = Immediate recall
F.R. = Free recall
C.R. = Cued recall
D.F.R. = Delayed free recall
D.C.R. = Delayed cued recall

Name:
Date:

BUSCHKE 16 (Version 2)

Semantic category	Target	Imm.R.	F.R.1	C.R. 1	F.R. 2	C.R. 2	F.R.3	C.R.3	D.F.R.	D.C.R.
Body part	Shoulder									
Vehicle	Yacht									
Bird	Crow									
Fruit	Coconut									
Toy	Frisbee									
Tool	Pliers									
Piece of furniture	Couch									
Vegetable	Spinach									
Flower	Tulip									
Animal	Lamb									
Clothing	Scarf									
Tree	Fir									
Musical instrument	Flute									
Fish	Sardine									
Profession	Painter									
Utensil	Whisk									
TOTAL										

TOTAL F.R. + C.R. ☐ ☐ ☐ ☐

Imm. R = Immediate recall
F.R. = Free recall
C.R. = Cued recall
D.F.R. = Delayed free recall
D.C.R. = Delayed cued recall

Name:
Date:

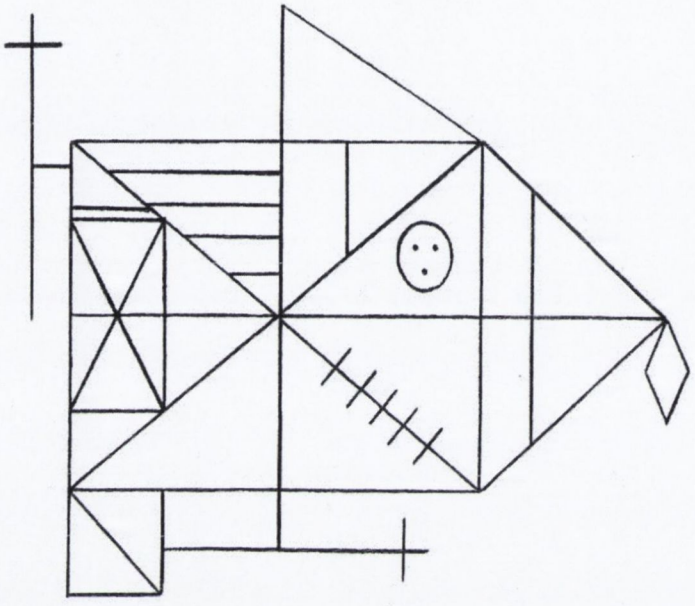
BUSCHKE 16 (Version 3)

Semantic category	Target	Imm.R.	F.R.1	C.R. 1	F.R. 2	C.R. 2	F.R.3	C.R.3	D.F.R.	D.C.R.
Profession	Cook									
Piece of furniture	Bookcase									
Utensil	Grater									
Tree	Cedar									
Body part	Nose									
Tool	Drill									
Flower	Daisy									
Fish	Trout									
Fruit	Pineapple									
Animal	Squirrel									
Musical instrument	Harp									
Vehicle	Helicopter									
Clothing	Shorts									
Bird	Duck									
Vegetable	Peas									
Toy	Puzzle									
TOTAL										

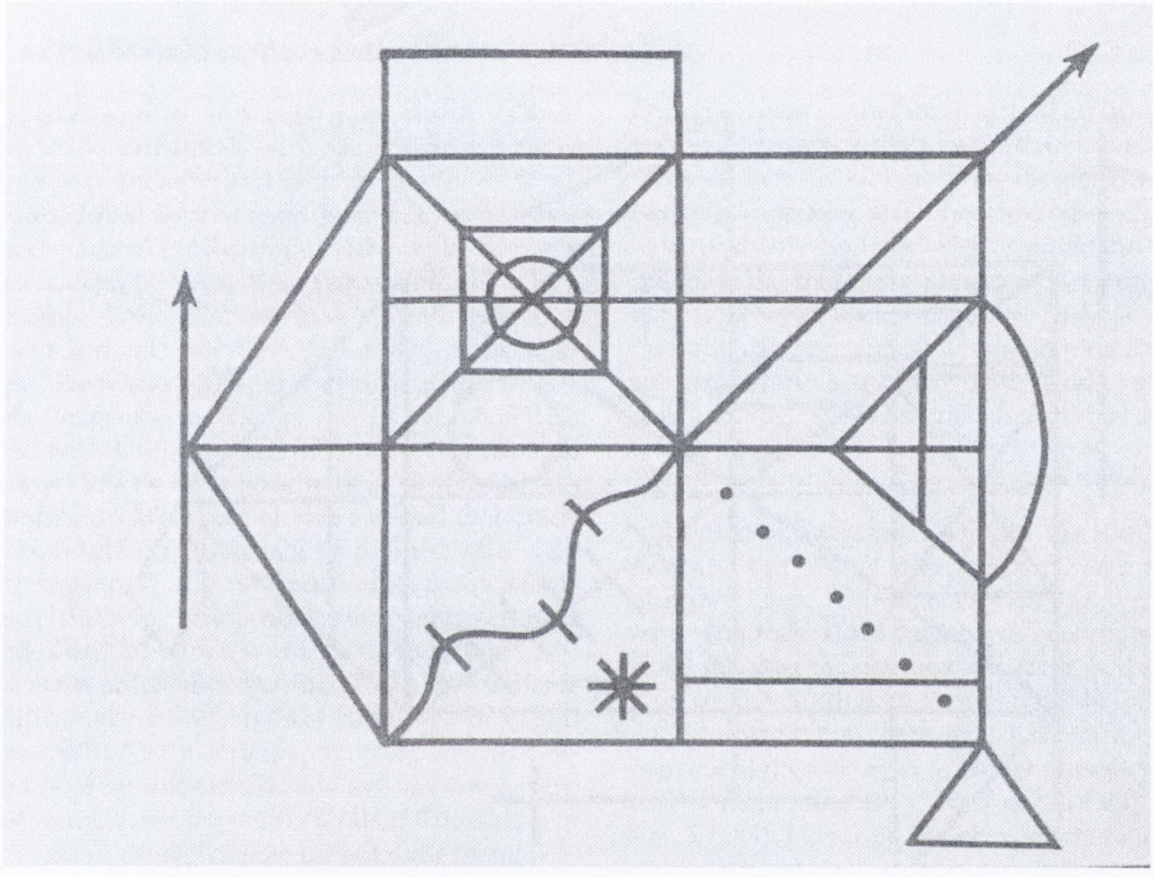
TOTAL F.R. + C.R. | | | | |

Imm. R = Immediate recall
F.R. = Free recall
C.R. = Cued recall
D.F.R. = Delayed free recall
D.C.R. = Delayed cued recall

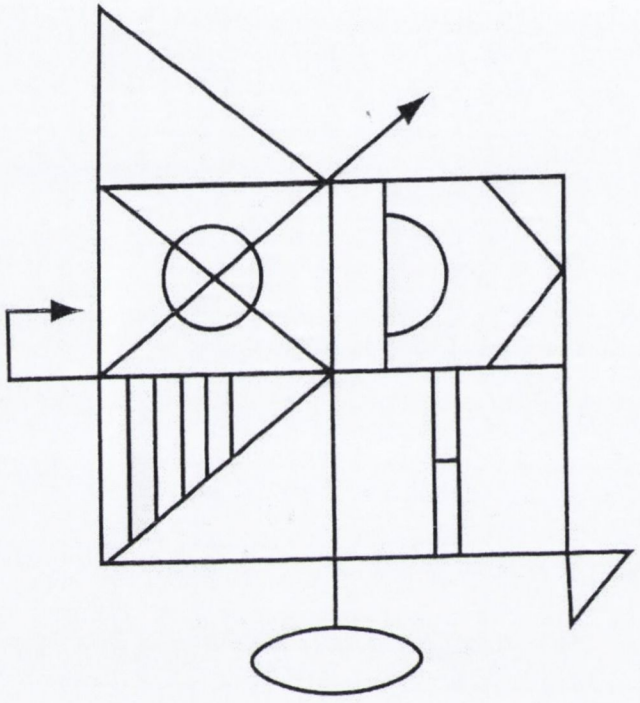
APPENDIX 13: REY-OSTERRIETH COMPLEX FIGURE



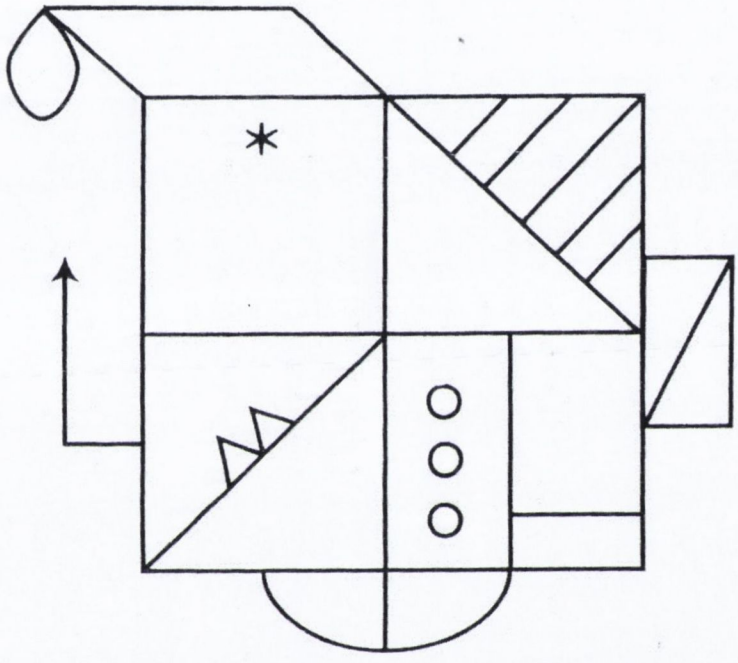
Taylor Complex Figure



Medical College of Georgia Complex Figure



Medical College of Georgia Complex Figure



APPENDIX 14/15: DIGIT SPAN FORWARDS AND BACKWARDS

Name/DOB Code ☐☐☐ ☐ ☐-☐ Date (mm/dd/yy) ☐☐ ☐☐ ☐☐

Digit Span Test (Form I)

Note—Discontinue after failure on both trials of any one level. Administer both trials, even if subject passes first trial.

Forward Span	pass ☐ fail ☐	score (0,1,2)	Backward Span	pass ☐ fail ☐	score (0,1,2)
				☐	
8—1—5	☐		5—1	☐	
2—5—9	☐	☐	6—9	☐	☐
4—9—6—1	☐		5—8—2	☐	
5—3—9—1	☐	☐	1—7—4	☐	☐
3—8—6—2—7	☐		7—2—9—5	☐	
7—6—2—3—8	☐	☐	9—7—3—5	☐	☐
4—2—6—7—3—8	☐		5—6—8—9—1	☐	
9—3—1—6—8—7	☐	☐	7—1—9—4—8	☐	☐
3—5—4—8—9—6—2	☐		1—5—3—2—9—6	☐	
1—5—8—7—2—3—9	☐	☐	4—1—7—8—3—9	☐	☐
7—1—6—8—2—4—3—5	☐		3—7—1—6—9—4—8	☐	
8—6—5—9—1—4—2—7	☐	☐	9—1—3—4—8—7—2	☐	☐
5—3—8—7—1—2—4—6—9	☐		4—8—5—6—3—1—2—9	☐	
3—1—7—9—5—4—8—2—6	☐	☐	2—5—8—4—3—7—6—1	☐	☐
Maximum Forward Span	☐		**Maximum Backward Span**	☐	
Total Score Forward		☐☐	**Total Score Backward**		☐☐

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Name/DOB Code ☐☐☐ ☐ ☐☐☐ Date (mm/dd/yy) ☐☐ ☐☐ ☐☐

Digit Span Test (Form II)

Note—Discontinue after failure on both trials of any one level. Administer both trials, even if subject passes first trial.

Digits Forward	pass ☐ fail ☐	score (0,1,2)	Digits Backward	pass ☐ fail ☐	score (0,1,2)
7—6—2	☐		9—7	☐	
3—4—9	☐	☐	3—4	☐	☐
3—2—7—6	☐		3—2—6	☐	
2—7—1—8	☐	☐	4—6—5	☐	☐
4—5—8—3—1	☐		6—9—8—4	☐	
8—3—1—4—9	☐	☐	4—2—1—3	☐	☐
6—7—5—8—3—2	☐		7—6—9—8—1	☐	
8—9—5—7—3—2	☐	☐	9—4—5—6—8	☐	☐
3—9—8—6—1—2—4	☐		1—7—9—8—3—6	☐	
8—2—4—6—9—5—7	☐	☐	6—4—5—1—8—2	☐	☐
3—2—9—1—5—4—8—7	☐		1—6—4—8—9—5—3	☐	
9—7—6—3—1—5—8—2	☐	☐	3—4—5—8—9—6—2	☐	☐
2—6—9—5—8—3—7—1—4	☐		4—5—9—2—8—1—6—3	☐	
4—9—7—3—6—1—5—8—2	☐	☐	1—5—6—2—8—7—3—4	☐	☐
Maximum Forward Span	☐		**Maximum Backward Span**	☐	
Total Score Digits Forward	☐	☐	**Total Score Digits Backward**	☐	☐

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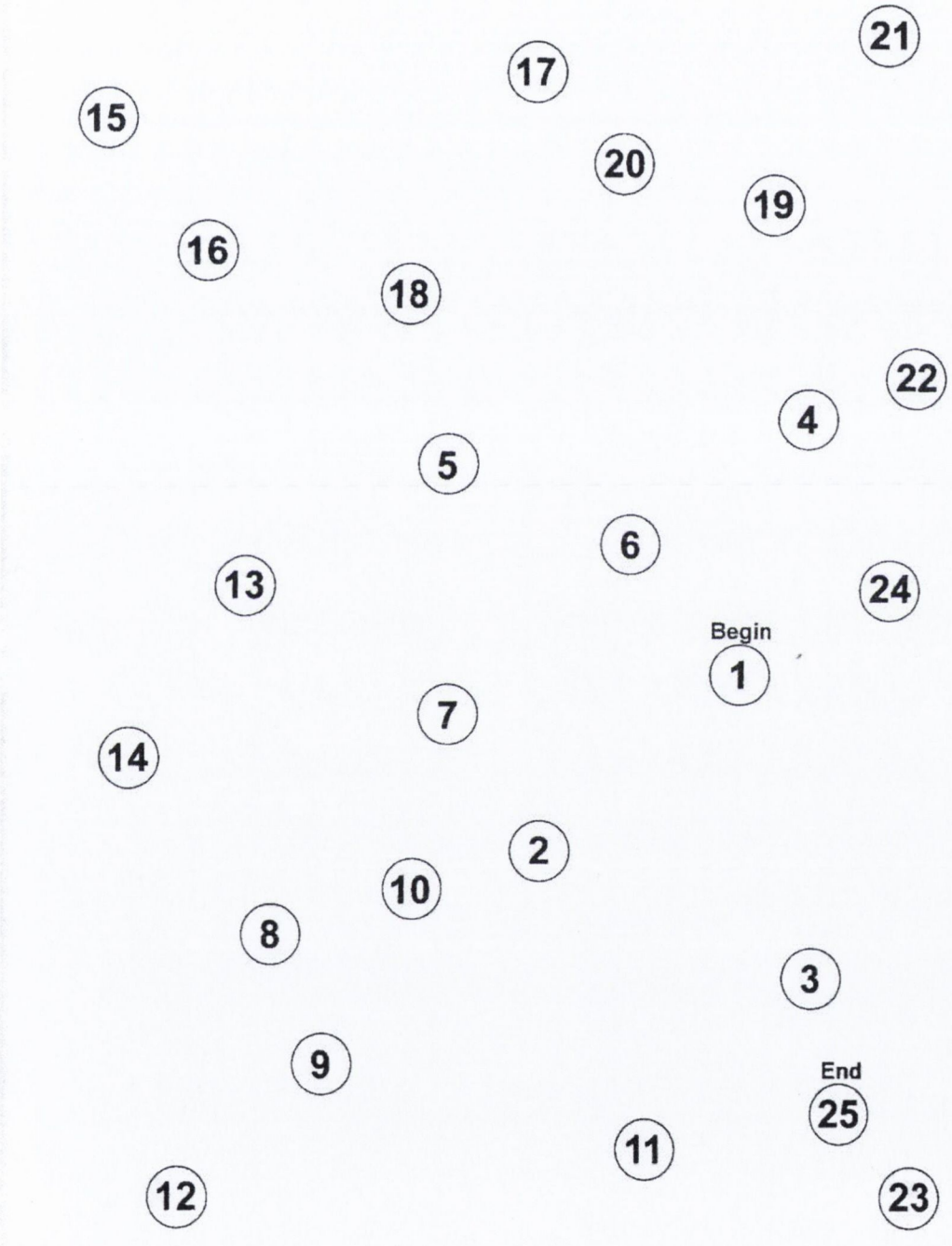
Name/DOB Code ☐☐☐ ☐ ☐☐☐ Date (mm/dd/yy) ☐☐ ☐☐ ☐☐

Digit Span Test (Form III)

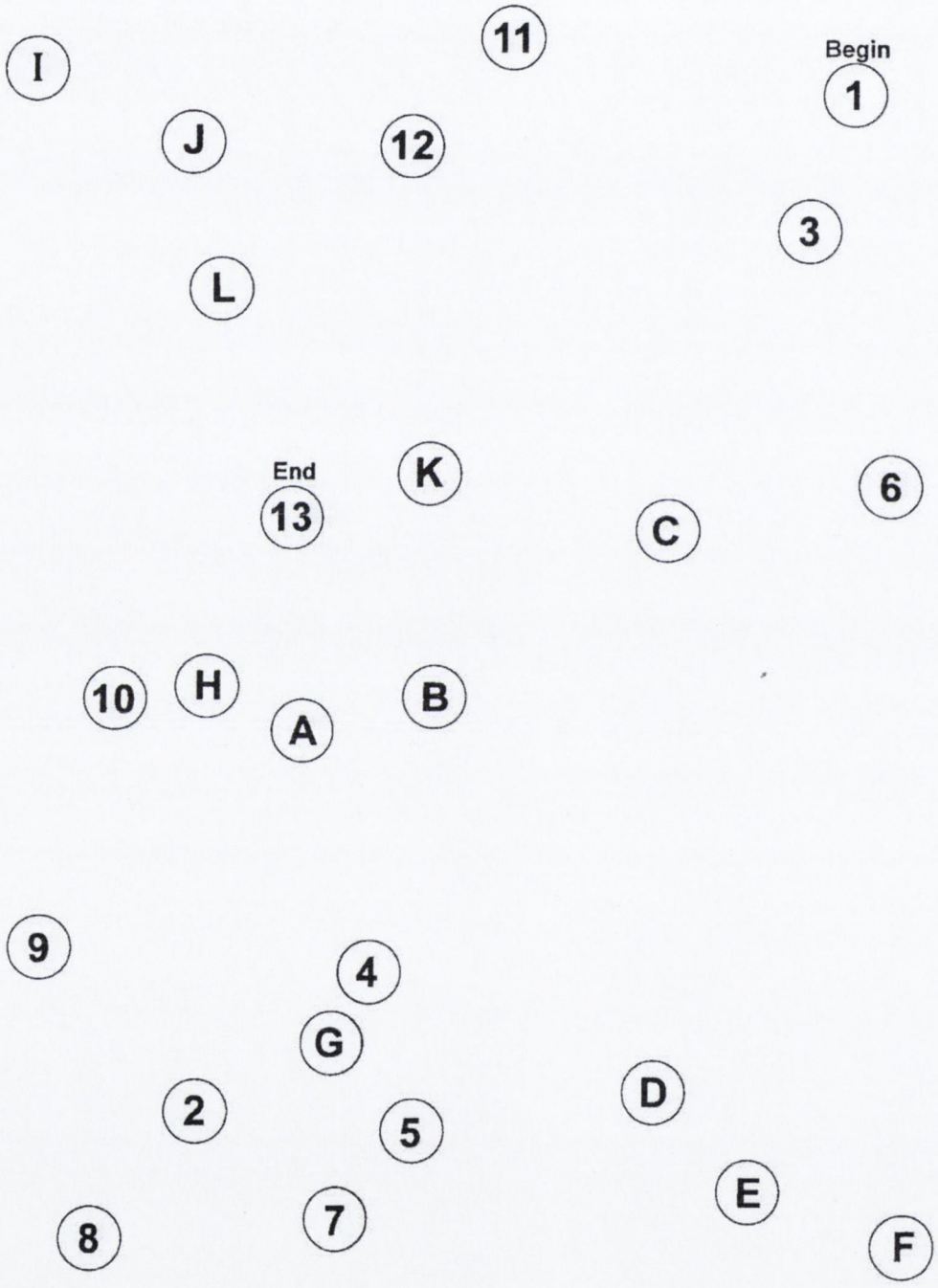
Note—Discontinue after failure on both trials of any one level. Administer both trials, even if subject passes first trial.

Digits Forward	pass ☐ fail ☐	score (0,1,2)	Digits Backward	pass ☐ fail ☐	score (0,1,2)
2—9—3	☐		8—7	☐	
5—2—1	☐	☐	6—2	☐	☐
9—1—2—4	☐		7—2—5	☐	
1—2—7—6	☐	☐	6—4—3	☐	☐
2—7—9—8—5	☐		4—1—5—7	☐	
4—7—5—6—8	☐	☐	9—3—6—5	☐	☐
3—4—9—5—2—6	☐		3—9—4—5—7	☐	
8—5—3—1—2—9	☐	☐	6—7—9—8—3	☐	☐
7—8—1—9—4—2—3	☐		2—8—4—7—1—3	☐	
9—6—3—2—7—5—4	☐	☐	3—1—5—9—8—7	☐	☐
8—3—6—2—1—5—4—7	☐		7—3—1—5—4—9—8	☐	
4—5—7—9—2—1—6—8	☐	☐	5—6—1—2—7—8—3	☐	☐
2—7—5—8—6—4—1—9—3	☐		6—4—8—7—5—3—1—2	☐	
7—1—3—9—4—2—5—6—8	☐	☐	1—7—3—6—2—8—5—9	☐	☐
Maximum Forward Span	☐		Maximum Backward Span	☐	
Total Score Digits Forward	☐	☐	Total Score Digits Backward	☐	☐

APPENDIX 16: TRAIL MAKING TEST PART A



APPENDIX 17 TRAIL MAKING TEST PART B



APPENDIX 18: THE GROOVED PEGBOARD TEST

Grooved Pegboard Test.

Pegboard is placed in mid-line with the subject so that the board is at the edge of the table and peg tray immediately above the board. The test is then explained:

THIS IS A PEGBOARD AND THESE ARE THE PEGS. (The examiner points out each and then picks up one of the pegs and continues.)

ALL THE PEGS ARE THE SAME. THEY HAVE A GROOVE, THAT IS, A ROUND SIDE AND A SQUARE SIDE AND SO DO THE HOLES IN THE BOARD. WHAT YOU MUST DO IS MATCH THE GROOVE OF THE PEG WITH THE GROOVE OF THE BOARD AND PUT THESE PEGS INTO THE HOLES LIKE THIS (Demonstrates by filling the top row. Afterwards remove the pegs and replace them in the tray.)

WHEN I SAY GO, BEGIN HERE AND PUT THE PEGS INTO THE BOARD AS FAST AS YOU CAN, USING ONLY YOUR RIGHT HAND. FILL THE TOP ROW COMPLETELY FROM LEFT TO RIGHT. DO NOT SKIP ANY , FILL EACH ROW THE SAME WAY.

(If necessary remind the subject that ONLY RIGHT HAND may be used. Subject should NOT PICK UP ANY DROPPED PEGS.)

Allow 3 minutes.

Things to record

Time to completion_____

No. of pegs dropped_____

No. completed in 3 mins_____

APPENDIX 19: THE MEM-DEP STUDY ETHICS APPROVAL (ST. PATRICK'S UNIVERSITY HOSPITAL)

St. Patrick's Hospital

Please reply to:
St. Patrick's Hospital, P.O. Box 136, James's St., Dublin 8.
Tel: 01 249 3200 Fax: 01 679 8865
www.stpatrickshosp.com

James V. Lucey
M.D. Ph.D. F.R.C.P.I. F.R.C.Psych.
Medical Director

CONFIDENTIAL

5th February 2008

Ms Martha Noone
Dept. Of Psychiatry
St Patrick's Hospital

Re: The Mem-Dep Study: Depression and Retrograde Memory
(Protocol number 01/08)

Dear Ms Noone,

Thank you for submitting changes to your application to the Research Ethics Committee at St Patrick's Hospital. The changes to Protocol 01/08 were considered by the Committee at the meeting on the 26th January, 2009. I am pleased to inform you that your study was fully approved by the Research Ethics Committee.

This approval is subject to full adherence with the terms and conditions set out in your research protocol and the condition that the researchers report back to the Research Ethics Committee no later than 12 months subsequent to this approval with a report on the progress of their research work.

If there are any material changes to Protocol 01/08 in the following 12 months you are required to contact the Research Ethics Committee for approval.

With best wishes.

Yours sincerely,

JAMES V. LUCEY MD.,Ph.D.,FRCPI.,FRCPsych.,
MEDICAL DIRECTOR

St. Edmundsbury,
Lucan, Co. Dublin.
Tel: 01 621 8200 Fax: 01 628 2979

Changing perceptions

APPENDIX 20: THE MEM-DEP STUDY ETHICS APPROVAL (TRINITY COLLEGE DUBLIN)

THE UNIVERSITY OF DUBLIN
TRINITY COLLEGE

SCHOOL OF MEDICINE
FACULTY OF HEALTH SCIENCES

Trinity College, Dublin 2, Ireland

Professor Dermot Kelleher, MD, FRCPI, FRCP, F Med Sci
Head of School of Medicine
Vice Provost for Medical Affairs

Tel: +353 1 896 1476
Fax: +353 1 671 3956
email: medicine@tcd.ie

Ms Fedelma McNamara
School Administrator

email: medschadmin@tcd.ie

Ms Martha Noone
Department of Psychiatry,
St Patrick's Hospital,
James's Street,
Dublin 8

Monday, 23rd March, 2009

Study: The mem-dep study - Depression and retrograde memory

Dear Applicant (s),

Further to a meeting of the Faculty of Health Sciences Ethics Committee held in January 2009, we are pleased to inform you that the above project has been approved without further audit.

Yours sincerely

Dr. Orla Sheils
Chairperson
Faculty of Health Sciences Ethics Committee

cc Professor Declan McLoughlin, Department of Psychiatry, St Patrick's Hospital, James's Street, Dublin 8

APPENDIX 21: MEM-DEP STUDY INFORMATION SHEETS

PARTICIPANT INFORMATION SHEET

The Mem-Dep Study:

Depression and Retrograde Memory

You are invited to take part in a research study. It is important for you to understand why this research is being carried out and what it will involve, before you decide whether you would like to take part. This Information Sheet has been written for you and it is essential that you read through it carefully and discuss it with one of the researchers or anybody you wish. Please ask whatever questions come to mind and particularly those that this Information Sheet may not answer. Further information about the study can be provided. Take time to decide whether or not you wish to take part.

PURPOSE OF THE STUDY:

The aim of this project is to study changes in cognitive function (mental activities such as thinking, perception, judgment, learning and memory) both *during* and *after* an episode of major depression. In particular we are interested in retrograde memory; this is a person's ability to recall events that occurred *in the past*. This will allow us to determine the types of cognitive and memory problems that can occur when someone is depressed. By conducting follow-up assessments over the course of one year we will then be able to determine whether any deficits remain when the depression has lifted following treatment.

We also wish to use these same assessments with people who are not depressed, so that we can see how much the performance of a depressed person differs to that of a non-depressed person. This will provide a clear picture of the extent of cognitive difficulties for someone suffering from depression.

A small number of studies have looked at how depression affects cognitive function, but to date results have proved inconclusive. However, some studies report deficits in attention and short-term learning and memory that persist when the depression has remitted. One study has shown that autobiographical retrograde memory function in remitted depressed patients was still

significantly lower than that of non-depressed people; autobiographical memory refers to memory of personal life events.

ASSESSMENTS:

Potential changes in clinical and cognitive function will be measured using a number of standard assessments. The clinical assessments are questionnaires that determine if the participant is suffering from depression. A number of questionnaires and tasks will be used to measure general cognitive function and in particular retrograde memory function. These assessments will be used at set time-points in the study in order to measure how function might change over time. As such, you will be asked to come back for assessment 2, 6 and 12 months after your initial assessment. This is to see if there are any changes in your performance over time.

In addition to undergoing clinical and cognitive assessment we would like to collect a blood sample at each of the four assessment sessions. The reason for the blood sample is to try to develop a simple blood test to predict the onset or relapse of a depressive episode. Currently there is no known measurable biological change in major depression that has proved of routine clinical value. In an effort to identify such a biomarker for depression we will use a technique called "proteomics" that will allow us to analyse up to several thousand proteins in the blood at one time and compare these between different depressed and non-depressed groups. Thus, the identification of a simple, reliable and readily accessible 'blood test' would be a very important clinical aid for diagnosing depression, measuring a patients' response to treatment, and identifying patients who are at risk of relapse.

We also wish to study how our genetic make-up can influence recovery from depression and memory function in depression. Again, this will involve analysis of your blood sample to look at normal genetic variations and also the activity of some of your genes that are known to be involved in mood and cognition.

WHY HAVE I BEEN CHOSEN?

You have been chosen because you have been referred for treatment for a depressive episode, and by comparing your scores on these assessments to a *non*-depressed person's score we can see what difficulties people who are depressed might have. The important information that we will gather from this study could lead to refinement of patient care during and after a depressive episode to ensure that any difficulties are not being left untreated.

DO I HAVE TO TAKE PART?

It is your decision whether you take part of not. If you do decide to get involved with the study, you will be given this Information Sheet to keep and asked to sign a Consent Form. You may withdraw from the study at any time

you wish and without giving a reason. This will not affect the care you receive from your doctor or any other person with whom you are involved.

WHAT WILL HAPPEN IF I AGREE TO TAKE PART IN THIS STUDY?

If you agree to help us, you will be interviewed by a member of our clinical research team who will carry out a standard diagnostic interview (to confirm a diagnosis of depression or establish that your mood is normal) plus a series of assessments to measure general cognitive and memory function. All of this should last about 2-3 hours but it will be possible to take some breaks. You will also be interviewed at 2, 6 and 12 months after your initial assessment. These follow-up assessments will be shorter than the first one and should last no more than 2 hours.

This research is being funded by the Health Research Board and St. Patrick's Hospital. At a later stage these results may form part of a collaborative study with researchers in Ireland and abroad.

WHAT WILL BE THE POSSIBLE BENEFITS OF TAKING PART?

This study will be of no direct benefit to you, but you will be helping us to refine our knowledge of the cognitive changes which take place across the timeline of a depressive episode, with a particular interest in determining whether any identified retrograde memory deficits remain present in depressed patients when the depression has remitted. If this is the case then this would lead to further refinement of after-care for patients who are recovering from a major depressive episode.

There will be a study newsletter for all participants and, if you wish, we will use this to keep you informed of the progress of the study in general.

WHAT ARE THE POSSIBLE DISADVANTAGES OF TAKING PART?

A possible disadvantage to you is the time it takes to be interviewed, completing questionnaires and assessments. To minimise any discomfort multiple breaks can be taken.

Other possible disadvantages are those associated with having a blood sample taken. This is a routine and safe procedure and you will probably already have experience of blood tests. Occasionally, minor bruising around the site from which the blood was drawn may occur, but this will quickly disappear. Very rarely, the site may become infected, but this is easily treated.

WILL MY TAKING PART BE CONFIDENTIAL?

Yes. All information collected about you during the course of the research will be kept strictly confidential. Your name will not be attached to any information about you that leaves the hospital. You will not be referred to by name in any articles/ presentations that arise from this study.

WHAT WILL HAPPEN TO THE RESULTS OF THE RESEARCH STUDY?

The results will be published in scientific journals and presented at conferences, again without any breach of confidentiality.

LEGAL ISSUES:

The researchers involved in this study are covered by standard medical malpractice insurance. Nothing in this document restricts or curtails your rights.

PERMISSION:

This study has been approved by the St. Patrick's Hospital Research Ethics Committee (Protocol no. xxx/08).

FURTHER INFORMATION:

If you would like to obtain further information about the nature of the study you can do so by contacting:

Prof Declan McLoughlin
Dept of Psychiatry
Trinity College Dublin
St Patrick's Hospital
James's Street
Dublin 8
Tel: (01) 2493385
E-mail:d.mcloughlin@tcd.ie

Thank you for your help with this project

PARTICIPANT INFORMATION SHEET

The Mem-Dep Study:

Depression and Retrograde Memory

You are invited to take part as a control participant in this research study. It is important for you to understand why this research is being carried out and what it will involve, before you decide whether you would like to take part. This Information Sheet has been written for you and it is essential that you read through it carefully and discuss it with one of the researchers or anybody you wish. Please ask whatever questions come to mind and particularly those that this Information Sheet may not answer. Further information about the study can be provided. Take time to decide whether or not you wish to take part.

PURPOSE OF THE STUDY:

The aim of this project is to study changes in cognitive function (mental activities such as thinking, perception, judgment, learning and memory) both *during* and *after* an episode of major depression. In particular we are interested in retrograde memory; this is a person's ability to recall events that occurred *in the past*. This will allow us to determine the types of cognitive and memory problems that can occur when someone is depressed. By conducting follow-up assessments over the course of one year we will then be able to determine whether any deficits remain when the depression has lifted following treatment.

We also wish to use these same assessments with people who are not depressed, so that we can see how much the performance of a depressed person differs to that of a non-depressed person. This will provide a clear picture of the extent of cognitive difficulties for someone suffering from depression.

A small number of studies have looked at how depression affects cognitive function, but to date results have proved inconclusive. However, some studies report deficits in attention and short-term learning and memory that persist when the depression has remitted. One study has shown that autobiographical retrograde memory function in remitted depressed patients was still significantly lower than that of non-depressed people; autobiographical memory refers to memory of personal life events.

ASSESSMENTS:

Potential changes in clinical and cognitive function will be measured using a number of standard assessments. The clinical assessments are questionnaires that determine if the participant is suffering from depression. A number of questionnaires and tasks will be used to measure general cognitive function and in particular retrograde memory function. These assessments will be used at set time-points in the study in order to measure how function might change over time. As such, you will be asked to come back for assessment at 6 and 12 months after your initial assessment. This is to see if there are any changes in your performance over time.

In addition to undergoing clinical and cognitive assessment we would like to collect a blood sample at each assessment. The reason for the blood sample is to try to develop a simple blood test to predict the onset or relapse of a depressive episode. Currently there is no known measurable biological change in major depression that has proved of routine clinical value. In an effort to identify such a biomarker for depression we will use a technique called "proteomics" that will allow us to analyse up to several thousand proteins in the blood at one time and compare these between different depressed and non-depressed groups. Thus, the identification of a simple, reliable and readily accessible 'blood test' would be a very important clinical aid for diagnosing depression, measuring a patients' response to treatment, and identifying patients who are at risk of relapse.

We also wish to study how our genetic make-up can influence recovery from depression and memory function in depression. Again, this will involve analysis of your blood sample to look at normal genetic variations and also the activity of some of your genes that are known to be involved in mood and cognition. If you do not wish to give a blood sample you will still be able to take part in the rest of the study.

WHY HAVE I BEEN CHOSEN?

You have been chosen because you *do not* suffer from depression, and by comparing your scores on these assessments to a depressed person's score we can see what difficulties people who are depressed might have. The important information that we will gather from this study could lead to refinement of patient care during and after a depressive episode to ensure that any difficulties are not being left untreated.

DO I HAVE TO TAKE PART?

It is your decision whether you take part of not. If you do decide to get involved with the study, you will be given this Information Sheet to keep and asked to sign a Consent Form. You may withdraw from the study at any time you wish and without giving a reason. This will not affect the care you receive from your doctor or any other person with whom you are involved.

WHAT WILL HAPPEN IF I AGREE TO TAKE PART IN THIS STUDY?

If you agree to help us, you will be interviewed by a member of our clinical research team who will carry out a standard diagnostic interview (to ensure that you are not depressed) plus a series of assessments to measure general memory and cognitive function. You will then be asked to give a blood sample. All of this should last about 2 hours but it will be possible to take some breaks. You will also be interviewed at 6 and 12 months after your initial assessment. These follow-up assessments will be shorter than the first one and should last no more than 2 hours.

The blood sample you give will be examined by research scientists at our laboratories in Trinity College Dublin and University College Dublin. These staff will only know the identity of your blood sample by a code number and the key to this code and any personal information will be kept confidentially by Professor Declan McLoughlin at St. Patrick's Hospital, Dublin.

This research is being funded by the Health Research Board and St. Patrick's Hospital. At a later stage these results and samples may form part of a collaborative study with researchers in Ireland and abroad.

WHAT WILL BE THE POSSIBLE BENEFITS OF TAKING PART?

This study will be of no direct benefit to you, but you will be helping us to refine our knowledge of the cognitive changes which take place across the timeline of a depressive episode, with a particular interest in determining whether any identified retrograde memory deficits remain present in depressed patients when the depression has remitted. If this is the case then this would lead to further refinement of after-care for patients who are recovering from a major depressive episode.

No individual protein result from the blood sample will be available from the study, to you or to anyone else.

There will be a study newsletter for all participants and, if you wish, we will use this to keep you informed of the progress of the study in general.

WHAT ARE THE POSSIBLE DISADVANTAGES OF TAKING PART?

A possible disadvantage to you is the time it takes to be interviewed, completing questionnaires and assessments. To minimise any discomfort, multiple breaks can be taken.

Other possible disadvantages are those associated with having a blood sample taken. This is a routine and safe procedure and you will probably already have

experience of blood tests. Occasionally, minor bruising around the site from which the blood was drawn may occur, but this will quickly disappear. Very rarely, the site may become infected, but this is easily treated.

WILL MY TAKING PART BE CONFIDENTIAL?

Yes. All information collected about you, during the course of the research, will be kept strictly confidential. Your name will not be attached to any information about you that leaves the hospital. You will not be referred to by name in any articles/ presentations that arise from this study.

WHAT WILL HAPPEN TO THE RESULTS OF THE RESEARCH STUDY?

The results will be published in scientific journals and presented at conferences, again without any breach of confidentiality.

LEGAL ISSUES:

The researchers involved in this study are covered by standard medical malpractice insurance. Nothing in this document restricts or curtails your rights.

PERMISSION:

This study has been approved by the St. Patrick's Hospital Research Ethics Committee.

FURTHER INFORMATION:

If you would like to obtain further information about the nature of the study you can do so by contacting:

Prof Declan McLoughlin
Dept of Psychiatry
Trinity College Dublin
St Patrick's Hospital
James's Street
Dublin 8
Tel: (01) 2493343
E-mail:d.mcloughlin@tcd.ie

Thank you for your help with this project

APPENDIX 22: MEM-DEP CONSENT

***The MEM-Dep Study*: Depression and retrograde memory function**

CONSENT FORM

The participant must complete this form herself/himself

PLEASE TICK YOUR RESPONSE IN THE APPROPRIATE BOX

- I have read and understood the attached Participant Information Leaflet..... Yes ☐ No ☐
- I have had the opportunity to ask questions and discuss the study ..... Yes ☐ No ☐
- I have received satisfactory answers to all my questions ..... Yes ☐ No ☐
- I have received enough information about this study ..... Yes ☐ No ☐
- I understand that I am free to withdraw from the study at any time without giving a reason and without this affecting my future medical care ..... Yes ☐ No ☐
- I agree to provide blood samples for analysis of protein expression..... Yes ☐ No ☐
- I agree to provide blood samples for genetic analysis ..... Yes ☐ No ☐
- I agree to take part in this study without prejudice to my legal/ethical rights. Yes ☐ No ☐

Participant's Signature: _____ Date _____

Participant's Name in Print: _____

Witness Signature: * _____ Date: _____

Witness' Name in Print: _____

Investigator's Signature: _____ Date: _____

Investigator's Name in Print: _____

Please attach the Participant Information Sheet to this Consent Form, ask the participant to sign and date it and, where appropriate, place a copy of both in the participant's case notes.

***Witness must be someone other than the Investigator.**

APPENDIX 23: THE EFFECT-DEP TRIAL ETHICS APPROVAL

(ST. PATRICK'S UNIVERSITY HOSPITAL)

St. Patrick's Hospital

Please reply to:
St. Patrick's Hospital, P.O. Box 136, James's St., Dublin 8.
Tel: 01 249 3200 Fax: 01 249 3417
www.stpatrickshosp.com

Patrick McKeon
M.D. F.R.C.P.I. F.R.C.Psych.
Medical Director

PRIVATE AND CONFIDENTIAL

Dictated: 8th October 2007
Typed: 8th October 2007

Our Ref: PMcK/lh

Prof. Declan McLoughlin
Consultant Psychiatrist
St. Patrick's Hospital

Re: Protocol No. 012/07 - The EFFECT-Dep Study: Enhancing the effectiveness of electroconvulsive therapy in severe depression and understanding its molecular mechanism of action

Dear Declan

Thank you for your response to the request for amendments to the above protocol. I note the amendments you have made and they are all in accord with those requested by the Research Ethics Committee.

The above protocol has now full Research Ethics Committee approval. The study will be subject to JCI accreditation audit.

With kind regards,

Yours sincerely,

Professor Patrick McKeon

Depart of Research Psychiatry
10 OCT 2007

St. Edmundsbury,
Lucan, Co. Dublin
Tel: 01 621 8200 Fax: 01 628 2979

Changing perceptions

APPENDIX 24: THE EFFECT-DEP TRIAL ETHICS APPROVAL (SJH/AMNCH HOSPITALS)

THIS NOTEPAPER MUST NOT BE USED FOR PRESCRIPTIONS OR INVOICING PURPOSES

SJH/AMNCH Research Ethics Committee Secretariat
Dan Lynch Ph: 4142860 email: Dan.Lynch@amnch.ie
Ursula Ryan Ph: 4142342 email: Ursula.Ryan@amnch.ie
Secretariat Fax 4142371

SJH/AMNCH
Research Ethics Committee
THE ADELAIDE & MEATH HOSPITAL, DUBLIN
INCORPORATING
THE NATIONAL CHILDREN'S HOSPITAL

TALLAGHT, DUBLIN 24, IRELAND
TELEPHONE +353 1 4142000

Professor David McLoughlin
Department of Psychiatry
Trinity College Dublin
St. Patrick's Hospital
James Street
Dublin 8

June 18th 2008.

REC reference: 2008/05/04 *(Please quote REC reference on all correspondence)*

Re: The *EFFECT –Dep Study:* Enhancing the Effectiveness of Electroconvulsive Therapy in Severe Depression and Understanding its Molecular Mechanism of Action.

Dear Professor McLoughlin,

The SJH / AMNCH Research Ethics Committee, at its meeting on May 28th 2008, agreed to give ethical approval to the above proposed study.

Yours sincerely,

Daniel R. Lynch,
Secretary,
SJH/AMNCH Research Ethics Committee

335703001

APPENDIX 25 EFFECT-DEP INFORMATION SHEET

INFORMATION SHEET

The EFFECT-Dep Study: enhancing the effectiveness of electroconvulsive therapy in severe depression and understanding its molecular mechanism of action

You are invited to take part in a research study. It is important for you to understand why this research is being carried out and what it will involve, before you decide whether you would like to take part. This Information Sheet has been written for you and it is essential that you read through it carefully and discuss it with your doctor, one of the researchers or anybody you wish. Please ask whatever questions come to mind and particularly those that this Information Sheet may not answer. Further information about the study can be provided. Take time to decide whether or not you wish to take part.

PURPOSES OF THE STUDY:

Bilateral and unilateral ECT
Electroconvulsive therapy (ECT) is the most powerful antidepressant treatment available and is often life-saving. In the standard form of ECT the treatment is applied to both sides of the forehead and this is called "bilateral ECT". There are, however, some concerns that bilateral ECT causes memory problems and that sometimes these problems may persist. In "unilateral ECT" the treatment is applied only to the right side of the head and this form of ECT causes less memory problems but is not as effective as bilateral ECT. However, small clinical trials have indicated that "high-dose" unilateral ECT, in which a greater electrical charge is used, may be as effective as standard bilateral ECT but have less memory side-effects.

How does ECT work?
The precise mechanism of action of ECT is not yet known. However, several lines of evidence now suggest that ECT works ultimately through increasing substances in the brain known as "growth factors". Increasing these growth factors results in the formation of new nerve cells within a region deep within the brain called the "hippocampus". The hippocampus is known to have important roles in regulating both mood and memory and one possibility is the ECT works by improving the function of the hippocampus.
Interestingly, similar effects are seen with antidepressant drugs, suggesting that there may be a common mechanism of action for all effective antidepressant treatments. Because the actual pathology of depression is also unknown, specific therapies have not been developed. However, it is generally agreed that understanding the molecular and cellular changes (such as those described in the previous paragraph) induced by ECT will improve understanding of how it works and in turn this information will help us to understand better what causes depression and lead to new treatments. One way to improve our understanding is to study the changes ECT induces in the expression of proteins (such as growth factors) and their genes and this can be analysed in blood samples. This is currently a subject of great research interest.

A "blood test" for depression

In addition, no known measurable biological change in major depression has yet proved of routine clinical value. Thus identification of a simple, reliable and readily accessible biomarker (i.e. a "blood test") would be an important clinical aid for diagnosis, measuring treatment response, and identifying patients at risk of relapse.

Proteins are the molecular "work horses" of all the cells within our bodies and if they are not working properly this can contribute to illness. However, it can be very difficult and time-consuming to identify which proteins may be malfunctioning, especially as our bodies make more than 25,000 different proteins each day! One way to overcome this problem, and rather than looking at each protein one-by-one, is to look at the global pattern of expression of all the proteins. This approach is called "proteomics" and is a very powerful tool to investigate disease. The "proteome" is the total complement of proteins produced; and studying the proteome is called "proteomics". We will use cutting-edge proteomic techniques that will allow us to analyse up to several thousand proteins at one time and compare these between different patient groups.

The purpose of this programme of work is to (1) improve ECT practice and (2) use ECT to help us better understand the biology of depression. We will carry out a definitive randomised controlled trial comparing bilateral and high-dose unilateral ECT, recruiting about 140 patients with severe depression. We will also characterise changes in global (i.e. the proteome) and individual protein/gene expression in blood samples obtained from patients recruited into the clinical trial.

WHY HAVE I BEEN CHOSEN?

You have been chosen because you have been referred for ECT for treatment of depression.

DO I HAVE TO TAKE PART?

It is your decision whether you take part of not. If you do decide to get involved with the study, you will be given this Information Sheet to keep and asked to sign a Consent Form. You may withdraw from the study at any time you wish and without giving a reason. This will not affect the care you receive from your doctor or any other person with whom you are involved.

WHAT WILL HAPPEN IF I AGREE TO TAKE PART IN THIS STUDY?

If you agree to help us, you will be interviewed by a member of our clinical research team who will carry out a standard diagnostic interview plus a series of assessments to measure the severity of your depression and general intellectual function, including memory and concentration. You will also be asked about your recent treatment and other services you have received in the previous 3 months. You will then be asked to give a blood sample. All of this should last about 2-3 hours but it will be possible to take some breaks.

If you decide to take part in this study, you will be allocated at random to having standard bilateral ECT or high-dose right-sided unilateral ECT. In order to reduce bias in the clinical trial, neither you nor your doctor will be informed which treatment you received until the trial is completed. However, if it was felt by your doctor that you were not improving enough you can be offered the alternative form of ECT.

We also wish to find out what the longer term outlook is following ECT and whether there are any side-effects which persist. Therefore we will want to repeat some of the assessments during your course of ECT and follow-up how you are doing over the next year. This will also entail our requesting some further blood samples.

The blood samples you give will be examined by research scientists at our laboratory in Trinity College Dublin. These staff will only know the identity of your blood sample by a code number and the key to this code and any personal information will be kept confidentially by Professor Declan McLoughlin at St. Patrick's Hospital, Dublin.

This research is being funded by the Health Research Board and St. Patrick's Hospital. At a later stage these results may form part of a collaborative study with researchers in Ireland and abroad.

WHAT WILL BE THE POSSIBLE BENEFITS OF TAKING PART?

This study will be of no direct benefit to you, but the results will improve clinical ECT practice and also help us understand better the molecular mechanism of action of ECT and lead to identification of candidate peripheral biomarkers for depression, treatment response and depression relapse. No individual protein/gene expression result will be available from the study, to you or to anyone else, and this study does not involve screening for genetic diseases.

There will be a study newsletter for all participants and, if you wish, we will use this to keep you informed of the progress of the study in general.

WHAT ARE THE POSSIBLE DISADVANTAGES OF TAKING PART?

Your own doctor will have already discussed the risks and benefits of ECT with you. In brief, the main medical risks of ECT are to do with having general anaesthesia and are essentially the same as having general anaesthesia for any other purpose such as a minor surgical procedure. There is no evidence to suggest that anaesthetic risk is any greater when having high-dose unilateral ECT. The other major risk associated with ECT is memory problems as already described above and one of the aims of this study is to try to reduce this.

Other possible risks are those associated with having a blood sample taken. This is a routine and safe procedure and you will probably already have experience of blood tests. Occasionally, minor bruising around the site from which the blood was drawn may occur, but this will quickly disappear. Very rarely, the site may become infected, but this is easily treated.

A possible disadvantage to you is the time it takes to be interviewed, completing questionnaires and assessments. To minimise any discomfort, multiple breaks can be taken.

WILL MY TAKING PART BE CONFIDENTIAL?

Yes. All information collected about you, during the course of the research, will be kept strictly confidential. Your name will not be attached to any information about you that leaves the hospital.

WHAT WILL HAPPEN TO THE RESULTS OF THE RESEARCH STUDY?

The results will be published in scientific journals and presented at conferences, again without any breach of confidentiality.

LEGAL ISSUES:

The researchers involved in this study are covered by standard medical malpractice insurance. Nothing in this document restricts or curtails your rights.

PERMISSION:

This study has been approved by the St. Patrick's Hospital Research Ethics Committee (Protocol no. 012/07).

FURTHER INFORMATION:

If you would like to obtain further information about the nature of the study you can do so by contacting:

Prof Declan McLoughlin
Dept of Psychiatry
Trinity College Dublin
St Patrick's Hospital
James's Street
Dublin 8
Tel: (01) 2493343
E-mail:d.mcloughlin@tcd.ie

Thank you for your help with this project

APPENDIX 26 EFFECT-DEP CONSENT

The EFFECT-Dep Study: enhancing the effectiveness of electroconvulsive therapy in severe depression and understanding its molecular mechanism of action

The participant must complete this form herself/himself

PLEASE TICK YOUR RESPONSE IN THE APPROPRIATE BOX

- I have read and understood the attached Participant Information Leaflet..... Yes ☐ No ☐
- I have had the opportunity to ask questions and discuss the study ..... Yes ☐ No ☐
- I have received satisfactory answers to all my questions ..... Yes ☐ No ☐
- I have received enough information about this study ..... Yes ☐ No ☐
- I understand that I am free to withdraw from the study at any time without giving a reason and without this affecting my future medical care ..... Yes ☐ No ☐
- I agree to provide blood samples for analysis of protein expression..... Yes ☐ No ☐
- I agree to take part in this study without prejudice to my legal/ethical rights. Yes ☐ No ☐

Participant's Signature: _____ Date: _____

Participant's Name in Print: _____ Date: _____

Witness Signature: * _____ Date: _____

Witness' Name in Print: _____

Investigator's Signature: _____ Date: _____

Investigator's Name in Print: _____

Please attach the Participant Information Sheet to this Consent Form, ask the participant to sign and date it and, where appropriate, place a copy of both in the participant's case notes.

***Witness must be someone other than the Investigator.**