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Neuropsychological and Electrophysiological Correlates of Self- and Error-Awareness in Focal Lesion Patients and Young Adults

by

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A dissertation submitted for the degree of Doctor of Philosophy of the University of Dublin, Trinity College, Dublin 2, Ireland.

This research was conducted in the School of Psychology and Trinity College Institute of Neuroscience.

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Declaration

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Summary

This thesis examines numerous aspects of deficit awareness, both among non-neurological participants and patients with circumscribed neural injury, in order to increase our understanding of the neuropsychological, neuroanatomical and electrophysiological bases of human self-awareness. Following a review of the extant literature on this topic, three studies are presented which adopt a multi-method approach to assessing self- and error-awareness, including the use of contemporary neuroscience paradigms that can be utilized in novel ways to explore clinically impaired self-awareness.

In order to understand disturbed self-awareness in clinical contexts, self-awareness must also be characterized in the normal population. Indeed, many studies assess self-awareness in a neurologically healthy control group for comparative purposes, yet few studies have attempted to delineate neuropsychological profiles for self-awareness levels in these participants. Chapter 2 therefore explores patterns of self-awareness in a large sample of neurologically healthy young adults, in order to investigate which neuropsychological functions may accompany different levels of awareness in the normal population. The results suggest that decreased sustained attention is a key neuropsychological marker for poor metacognitive awareness, which implicates frontal lobe functioning in self-awareness among young adults.

Chapter 3 directly examines the contribution of left and right frontal cortices to self-awareness, by measuring metacognitive, online emergent and online anticipatory awareness in four patient groups: those with left and right frontal,

as well as left and right non-frontal focal cortical lesions. Results show that both left and right frontal injury impairs metacognitive awareness. Additionally, right frontal lesion patients show a significant impairment in online emergent awareness of errors, and a reduced psychophysiological responsiveness to these errors, during a simple sustained attention task. Left frontal lesion patients, by contrast, showed that their capacity to monitor errors during a task was adequate: when asked to estimate their performance on simple cognitive tasks, they initially over-estimated their performance, but provided accurate estimates upon task completion. These findings point to the importance of the right frontal cortex in monitoring performance in a sustained manner, and providing top-down control over psychophysiological responses to erroneous responses.

The study reported in Chapter 4 employs Event-Related Potentials (ERPs) to examine the effects of frontal and non-frontal cortical lesions on a number of electrophysiological responses commonly observed after participants commit an erroneous response on a cognitive task. Frontal lesion patients showed no distinction between the early electrophysiological negativities following correct and incorrect responses. Non-frontal lesion patients, however, showed significantly lower awareness levels than frontal lesion patients and controls, and this behavioural result was accompanied by a reduced Error Positivity (Pe), an ERP marker for errors that reach conscious awareness.

Chapter 5 provides a discussion and integration of these findings with theoretical models, and suggests future research to address the questions arising from these studies.

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Hoerold, D., Pender, N. & Robertson, I.H. (submitted). The Neural Basis of Self-Awareness – Different Roles for Left and Right Prefrontal Cortex. *Brain.*

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List of Abbreviations

ACA	Anterior Cerebral Artery
ACC	Anterior Cingulate Cortex
AVM	Arteriovenous Malformation
AD	Alzheimer's Disease
CBD	Corticobasal Degeneration
CDIM	Comprehensive Dynamic Interactional Model
CFQ	Cognitive Failures Questionnaire
CT	Computed Tomography
DART	Dual Attention to Response Task
DTI	Diffusion Tensor Imaging
EAT	Error Awareness Task
EEG	Electroencephalography
ERN	Error-Related Negativity
ERP	Event-Related Potential
fMRI	Functional Magnetic Resonance Imaging
FrsBe	Frontal Systems Behavior Scale
FTD	Frontotemporal Dementia
HADS	Hospital Anxiety and Depression Scale
HD	Huntington's Disease
HI	Head Injury
IQ	Intelligence Quotient
ISI	Inter-Stimulus Interval
LF	Left Frontal
LNF	Left Non-Frontal

LPFC	Lateral Prefrontal Cortex
μS	Micro Siemens
μV	Micro Volts
MCA	Middle Cerebral Artery
MET	Measure of Empathic Tendency
MRI	Magnetic Resonance Imaging
NART-R	Revised National Adult Reading Test
Ne	Error (-Related) Negativity, see also ERN
PCA	Posterior Communicating Artery
PCRS	Patient Competency Rating Scale
PD	Parkinson's Disease
Pe	Error Positivity
PFC	Prefrontal Cortex
PSP	Progressive Supranuclear Palsy
RCZ	Rostral Cingulate Zone
RF	Right Frontal
RNF	Right Non-Frontal
R-SAT	Revised Strategy Application Task
SART	Sustained Attention to Response Task
SCR	Skin Conductance Response
SOPT	Self-Ordered Pointing Task
SPECT	Single Photon Emission Computed Tomography
TBI	Traumatic Brain Injury
TMT	Trail Making Test
WMS III	Wechsler Memory Scale (3rd Edition)

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Chapter 1 : General Introduction

1.1 Why Self-Awareness ?

Interest in the study of human self-awareness has increased greatly over the past 20-30 years, among researchers, philosophers and clinicians alike, which to some degree reflects an increased general effort to link brain states to conscious feeling and knowing states. The possibilities for exploring such links now exist in an unprecedented way, with modern neuroscience techniques advancing ever more rapidly. The search for the properties of the human brain that make conscious self-awareness possible is not only an intriguing philosophical enterprise: it is also relevant to a number of practical and clinical problems. Most of these become apparent when the capacity for self-awareness fails, as can be the case in many neuropsychological patient groups, including those suffering from traumatic brain injury (TBI), neurodegenerative disease and dementia, neuropsychiatric and neurodevelopmental disorder, and localised neural injury. It is the latter that will be the focus of the present thesis, in addition to a brief exploration of awareness of behaviour among neurologically healthy, young adults.

Injury or dysfunction of the human brain can bring about a broad range of cognitive, behavioural and emotional changes. Standard neuropsychological assessment aims to evaluate several categories of mental function, in order to infer the nature, scope and implications of such brain dysfunction. Typically, a

clinician will assess cognitive functions such as orientation and attention, memory, sensory, perceptual and motor abilities, emotional and personality variables, language, executive functions, with additional probing for specific functional aspects if individually required (Lezak, Howieson, & Loring, 2004). Self-awareness assessment is typically not included in standard evaluations (Bergquist & Malec, 2002), most likely due to the shortage of standardized measures available to clinicians. For clinical interventions and rehabilitation planning, this is particularly problematic. In fact, many investigators have argued that without accurate assessment of self-awareness, intervention efforts at the post-acute stage of brain injury are likely to be ineffective (Crosson et al., 1989). At best, short-term improvements may be observed within treatment settings, but fail to generalize to improved day-to-day functioning (Gordon, 1987).

In Alzheimer's Disease (AD), impaired self-awareness along with behavioural disturbances such as excessive disinhibition, contributes significantly to caregiver burden (Rymer et al., 2002), independently of dementia severity (Seltzer, Vasterling, Yoder, & Thompson, 1997). Without considerable social support, caregivers of TBI survivors experience increased distress long after the injury itself, if a patient fails to show awareness of his/her deficits (Ergh, Rapport, Coleman, & Hanks, 2002).

The issue of insight and preserved self-awareness is also problematic in medico-legal contexts, where immediate treatment of acute neural injury may be refused by a patient on the basis of his/her lack of awareness of the condition (Katz & Segal, 2004). In degenerative, psychiatric or chronic

conditions where independent living is no longer an option, insight becomes an important component of the 'capacity to consent' when hospitalization is required (e.g. Mukherjee & Shah, 2001). With populations aging steadily world-wide, and survival rates of brain injury constantly increasing, these concerns are likely to gain importance in the future of healthcare and medico-legal professions.

In the following sections, self-awareness will be discussed from clinical and cognitive neuroscience perspectives. First, a brief historical overview of the topic will be provided, followed by an introduction to the definitions and methods used in self-awareness research, a summary of previous findings regarding neuropsychological and neuroanatomical correlates of self-awareness, and an overview of the most influential theoretical models. The final section will outline the aims and structure of the present dissertation.

1.2 Disturbed Self-Awareness as a Disorder: A Brief Historical Overview

The first written record describing unawareness of an illness appears in the Moral Epistles of Seneca the Younger (ca. 4BC – 65AD), in the form of an anecdote about a servant who appeared to have no knowledge of her blindness (cited in Bisiach & Geminiani, 1991, p. 17). However, it was not until the end of the 19th century that detailed clinical descriptions began to emerge, and unawareness began to be recognized as a syndrome of brain dysfunction in its own right. A number of prominent neurologists and psychiatrists in continental Europe published case reports of patients who presented with a distinct lack of awareness about their condition, which ranged from cortical blindness and word deafness (Anton, 1899; von Monakow, 1885) to somatosensory dysfunction and paralysis (Anton, 1893, 1898; Pick, 1898). The most important conclusions emerging from these early descriptions was that no single impairment could account for these observations, as clinicians frequently emphasised their patients' preserved reasoning and intellectual abilities. These studies represent the first attempts to associate neural insult with unawareness of resulting deficit, and unawareness of cortical blindness is still referred to as "Anton's Syndrome" today, in honour of these earliest case studies.

In 1913, Hermann Zingerle reported on a patient with left hemiplegia and hemineglect, who temporarily believed that the left side of his body was another person lying in his bed (Zingerle, 1913), describing the syndrome as a local neurological disorder of mental representation and consciousness. Finally, in 1914, Josef François Babinksi coined the terms "anosognosia" to denote the unawareness of a paralysis of the limb, and "anosodiaphoria" to denote the

lack of concern some patients showed for their hemiplegia (Babinksi, 1914), noting the frequent involvement of right hemisphere lesions in both conditions (Papagno & Vallar, 2003). The years following Babinski's influential discussion in 1914 saw a number of similar clinical case studies or small series of cases published, including one noteworthy case where the patient's premorbid psychological state was known to clinicians, and was considered "unchanged" since her stroke, except for her persistent unawareness of hemiplegia, lasting until her death 20 years later (Joltrain, 1924). In the first report of a series of patients by Von Hagen & Ives (1937), attention was drawn to the *specificity* of anosognosia, with one patient showing awareness of her memory impairment and left upper limb hemiplegia, but lack of knowledge that her lower limb was also paralyzed. Thus, the first half of the 20th century showed an increasing number of fascinating anecdotal case reports, describing unawareness of deficit in a number of neurological patients, with a steady trend towards group studies in order to accrue clinical knowledge about the phenomenon and delineate its characteristics.

Following a series of studies published in the first monograph on the topic in 1955 (Weinstein & Kahn, 1955), the number of publications in this field declined somewhat, and it was not until the 1980s that larger-scale patient studies became a frequent occurrence. Over the past 30 years, self-awareness research has shifted in focus from qualitative, anecdotal reports to more systematic quantitative approaches, increasingly incorporating theoretical frameworks to account for present and previous observations in clinical populations. These models and their influence will be discussed in Section 1.6 below.

Researchers have also began to turn their interest to self-related processing in healthy participants. The search for the neural correlates of conscious self-awareness is in its infancy; however, the techniques of the modern cognitive neurosciences such as functional Magnetic Resonance Imaging (fMRI), Positron Emission Tomography (PET), Single Photon Emission Computed Tomography (SPECT) and Electroencephalography (EEG), increasingly allow the study of human self-awareness from new perspectives. Moreover, these techniques can be used to complement more traditional approaches in patient studies, as will be demonstrated throughout the research presented in this dissertation.

1.3 Defining and Measuring Self-Awareness

1.3.1 Terminology

Self-awareness, along with other closely-related concepts that centre around 'consciousness', lies at an intersection of a number of fields, including neuroscience, psychology, philosophy, the arts, and theology (Zeman, 2006). This means that multiple explanatory frameworks may exist which do not necessarily speak to each other. Even though the considerations which have arisen from the 'philosophy of mind'- approach have made rich contributions to the science of brain-behaviour relationships (e.g. Branquinho, 2001), the present dissertation will intentionally neglect philosophical and spiritual issues of "subjectivity", and focus on neurological and neuropsychological aspects of impaired self-awareness instead.

Impaired awareness of deficits can be defined as the inaccurate appraisal of one's behavioural, cognitive or emotional dysfunctions, which are obvious to other observers, such as family members, caregivers or clinicians. Kortte & Wegener (2004) have provided a useful summary and discussion of the various terms which have been used to refer to unawareness phenomena throughout the literature, including *denial of illness, anosognosia, lack of insight, lack of self-awareness, imperception of disease and unawareness of deficit.* These have sometimes been used interchangeably, despite certain conceptual differences, thereby adding to the difficulty of reconciling diverse findings between studies. For the purpose of the present thesis, *denial* (of illness or otherwise) is

considered a mechanism with primarily psychological aetiology, and will not be the focus of the following series of studies. Additionally, it is noteworthy that the term *anosognosia* is sometimes used in the literature to refer to specifically to unawareness of hemiplegia, in the conceptual sense in which the term was first introduced by Babinksi in 1914. The remaining terms, *unawareness of deficit, lack of self-awareness/insight,* and *imperception of disease* all refer to a lack of acknowledgement or under-estimation of a deficit in sensory, perceptual, cognitive, behavioural, or affective functioning arising from neural defect (e.g. Orfei, Robinson, Prigatano et al., 2007). Throughout this dissertation, the terms *unawareness,* and *(lack of) self-awareness* will be used, to allow inclusion of awareness of behaviours in healthy, non-neurological participants.

1.3.2 The Measurement of Self-Awareness

Perhaps the single most challenging aspect of self-awareness research remains the problem of measurement. Even though in recent decades many conceptual and methodological advances have been made, self-awareness remains a phenomenon which must be measured indirectly, since no contemporary method allows investigators to directly measure a participant's subjective experience (Prigatano, 2003). Each individual method of assessment has unique limitations. The following is a review of the available methods and the concerns associated with each of them.

In many early case studies, a lack of self-awareness was established by the clinician who diagnosed the neurological deficit, and evaluated the patients' knowledge of this deficit. An extension of such a method is the use of a questionnaire to probe patients' perception of their condition, and compare the resultant score with performance data (e.g. Deaton, 1986) or a clinician's judgement (e.g. Azouvi et al., 1996; Starkstein, Fedoroff, Price, Leiguarda, & Robinson, 1992). A small number of standardized interview schedules have been developed, which can be adjusted to individual patient needs (e.g. Anderson & Tranel, 1989; Fleming, Strong, & Ashton, 1996; Simmond & Fleming, 2003; Wise, Ownsworth, & Fleming, 2005). An obvious drawback to such a method is the reliance on the clinicians' expertise, which may fail to include more subtle aspects of individual patients' behaviour that can often only be captured through extensive observation of every-day activities. Furthermore, this method makes comparison of studies difficult, since clinicians' evaluations may vary greatly between studies. Lastly, such methods have increasingly been criticised for producing a limited number of awareness categories, such as "full", "shallow" or "no awareness" (e.g. Starkstein, Jorge, Mizrahi, & Robinson, 2006). Therefore, this measure is probably most useful in a clinical or rehabilitation setting, where experienced professionals can make an informed decision about the degree of impairment in self-awareness.

A related approach is the comparison of questionnaire scores obtained from patients themselves and those of family members or caregivers, or other 'significant others' in the patients' lives (e.g. Grace, Stout, & Malloy, 1999; Prigatano & Fordyce, 1986). This method remains the most frequent in research contexts, since it is relatively quick and easy to obtain (Fleming et al.,

1996). It allows for awareness of individual functions to be extracted, and represents a more quantitative approach to self-awareness research. However, the ratings obtained from an informant are likely to be influenced by a number of factors beyond the researcher's control, such as emotional state, psychological denial, or indeed a caregiver's heightened sensitivity to symptoms, after a clinical diagnosis has been made (e.g. Starkstein et al., 2006). In an attempt to address this limitation, Snow and colleagues assessed awareness in dementia patients in relation to both informant and clinician ratings (Snow et al., 2004). While this combined method promises to provide a more complete view of patients' knowledge and lack thereof, it is not useful for patients who are not under clinical care, as for example in non-acute cases of neurological injury or illness. Thus, for research with patients who live relatively independent in the community, discrepancy between patient ratings and those of family members may be the only option, in which case the use of multiple questionnaires and additional assessment is most certainly required.

More recently, in an attempt to examine self-awareness from a more cognitive perspective, researchers have begun to explore patients' estimates of cognitive performance, prior to and/or following a cognitive task (Barrett, Eslinger, Ballentine, & Heilman, 2005; Fischer, Trexler, & Gauggel, 2004; Marcel, Tegner, & Nimmo-Smith, 2004; O'Keeffe, Dockree, Moloney, Carton, & Robertson, 2007; O'Keeffe, Murray et al., 2007). Participants are generally considered to lack awareness when they grossly over-estimate how well they will perform. Such an approach also allows the possibility to examine patients' ability to adjust their estimate immediately after being confronted with their own performance, and results can easily be integrated into theoretical

frameworks proposed in recent years. While this approach is advantageous because it does not rely on an informant to assess a patient's level of functioning, there remains concern about the extent to which an accurate performance prediction is possible by any participant, given that the kinds of tasks involved are usually entirely new to participants.

Lastly, the role of conscious awareness is increasingly gaining importance for cognitive neuroscientists, with particularly promising advances in the area of cognitive control and error monitoring. The processes involved in detecting, correcting and minimizing errors were initially investigated by Rabbit during the 1960s (e.g. Rabbit, 1966) and interest re-emerged during the 1990s, when a number of electrophysiological responses were identified which can be linked specifically to the processing of action errors (see Chapter 5 for a more detailed review). Clarification of the precise role of *awareness* in such error processing, for example during choice reaction time tasks, is a major challenge in contemporary neuroscience. It is hoped that the results of such error processing studies can increase our understanding of the processes which lead to disturbed deficit awareness in clinical patient groups (e.g. Hart, Giovannetti, Montgomery, & Schwartz, 1998). Due to their excellent temporal resolution, electroencephalography (EEG) measurements have also recently been used to investigate the differences in time course between the *intention* to perform motor actions, and conscious awareness of the *execution* of such actions (e.g. Blakemore & Frith, 2003; Gold, Adair, Jacobs, & Heilman, 1994). This has produced a number of working hypotheses regarding the nature of abnormal action awareness in patients with schizophrenia, phantom limbs and parietal lobe lesions (Blakemore, Wolpert, & Frith, 2002; Frith, Blakemore, & Wolpert,

2000; Sirigu et al., 2004). Lastly, recent novel approaches to self-awareness also make use of the fMRI technique to examine the neural correlates of self-recognition (Keenan, Nelson, O'Connor, & Pascual-Leone, 2001), as well as other paradigms involving judgements pertaining to 'self' and 'other', such as theory-of-mind tasks (Platek, Keenan, Gallup, & Mohamed, 2004). It should be noted, however, that such studies have been criticised for reflecting only ancillary self-awareness processes, rather than conscious self-awareness per se (e.g. Morin, 2007).

In summary, a number of methods are available to examine self-awareness deficits, with recent neuroimaging and other technological developments promising more sophisticated and accurate measures in the future. An important aspect for assessing self-awareness, however, remains the exact characterisation of the function(s) which participants should be aware of. Additionally, despite the methodological advances documented above, the majority of studies to date have used one single method of assessing self-awareness. This is problematic since, as the following section will illustrate, impaired self-awareness is a complex and multifaceted phenomenon, which most likely cannot be adequately characterised with a singular score. Developing and refining new assessment methods is therefore crucial for this field, as is the use of a multidimensional examination of impaired self-awareness.

1.4 Characteristics of Impaired Self-Awareness in Clinical Groups

Due to the difficulties inherent in self-awareness research outlined above, reports describing the neuropsychological correlates of self-awareness are inconsistent, and in many cases the characteristics of the disorder may be specific to individual patient groups. Many authors have commented on the lack of clear trends in available data, and have called for studies to make use of more specific theoretical frameworks (e.g. Clare, 2004). The following is a review of the most salient features reported throughout the literature.

Among TBI patients, up to 97% may show residual awareness deficits, even in post-acute stages (Sherer, Bergloff et al., 1998), with the most conservative estimates still reaching 30% (Prigatano & Altman, 1990). Paradoxically, in one study, patients were shown to exhibit a "hyperawareness" of their symptoms, possibly due to the very mild nature of their injury (Coolidge, Mull, Becker, Stewart, & Segal, 1998). Severity of injury is often seen to be related to impaired self-awareness (e.g. Leathem, Murphy, & Flett, 1998; Prigatano & Altman, 1990; Sherer, Boake et al., 1998), however, not all studies have confirmed this relationship (e.g. Allen & Ruff, 1990; O'Keeffe, Dockree et al., 2007), with some studies showing the opposite effect (Sawchyn, Mateer, & Suffield, 2005; Sherer, Boake et al., 1998). TBI patients may more readily acknowledge behavioural limitations and deficits in everyday activities than higher level cognitive and emotional functions, such as abstract problem solving, planning and complex social interactions (Prigatano, 1996a). There is no clear neuropsychological profile which predicts impaired self-awareness, though executive dysfunction is rather frequently implicated in the disorder

(Coben, Boksenbaum, & Kulberg, 1995; Hart, Whyte, Kim, & Vaccaro, 2005; Noe et al., 2005; Ownsworth, McFarland, & Young, 2002), even though replication of such effects is not always successful (Bogod, Mateer, & MacDonald, 2003; Trudel, Tryon, & Purdum, 1998). Some studies have pointed to memory abilities as correlates or predictors of self-awareness deficits (Cocchini, Beschin, & Sala, 2002; Noe et al., 2005; Trudel et al., 1998). Sustained attention abilities have also been implicated (McAvinue, O'Keeffe, McMackin, & Robertson, 2005; O'Keeffe, Murray, et al., 2007). The inconsistencies are likely to arise from two sources: Firstly, self-awareness was assessed in different ways across these studies, making comparisons difficult. Secondly, TBI is frequently associated with diffuse cerebral injury, leading in turn to a multitude of cognitive, behavioural and emotional symptoms. Although the frontal and temporal lobes are seen to be most at risk (e.g. Ponsford, 1995), TBI is known to produce cascading neuropathological events which often go unnoticed at standard radiological examinations (e.g. Huisman et al., 2004). These two factors make it difficult to generalize findings from this patient group, especially since many studies fail to include a clinical control group for comparison, and can therefore only establish little more than that traumatic neural injury can be associated with impaired self-awareness.

In schizophrenia and other psychiatric patient groups who experience psychosis as part of their disease, some support exists that impaired self-awareness is related to a concurrent impairment of the executive functions (Cooke, Peters, Kuipers, & Kumari, 2005; Flashman, 2004; Morgan & David, 2004). However, several studies have also noted a relationship between memory function and awareness (Cuesta & Peralta, 1994; Marks, Fastenau,

Lysaker, & Bond, 2000), as well as general intellectual ability and awareness (David et al., 1995; Lysaker & Bell, 1994; Young, Davila, & Scher, 1993). Overall, the relationship between executive function and self-awareness appears to be the most robust finding, further evidenced by the fact that the effect persists when potentially confounding factors – such as IQ - are controlled for (Lysaker & Bell, 1994; Morgan & David, 2004). Interestingly, McEvoy et al. (1996) report an association between tests of left parietal lobe function and insight scores, while no such correlation emerged for tests of right parietal function. Two reports have also pointed to the importance of attentional impairment for impaired awareness in schizophrenia (Lysaker & Bell, 1994; Marks et al., 2000), which may arguably contribute to the more frequently reported finding of executive dysfunction. Thus, in summary, the search for the neuropsychological correlates of impaired self-awareness in schizophrenia has yielded variable results, which is most likely attributable to differences in key measurements of self-awareness, as well as inconsistencies in neuropsychological test batteries administered. Furthermore, cognitive processes in psychosis are altered in a number of ways, making it difficult to separate out individual contributors to a complex phenomenon such as disturbed self-awareness.

Among patients suffering from dementia and lack of awareness – including, for example, up to 20% of patients with Alzheimer's Disease (e.g. Migliorelli et al., 1995) - the search for a general profile of neuropsychological performance has also yielded few consistent findings. Domain-specificity of unawareness has been demonstrated, by showing dissociations between awareness of cognitive and behavioural symptoms (Starkstein, Sabe, Chemerinski, Jason, &

Leiguarda, 1996). Severity of dementia and self-awareness have sometimes shown to be negatively correlated (Lopez, Becker, Somsak, Dew, & DeKosky, 1994; Mangone et al., 1991; Migliorelli et al., 1995; Starkstein et al., 1996; Sultzer, Levin, Mahler, High, & Cummings, 1992; Verhey, Rozendaal, Ponds, & Jolles, 1993), but this effect has not consistently been replicated (Debettignies, Mahurin, & Pirozzolo, 1990; Feher, Mahurin, Inbody, Crook, & Pirozzolo, 1991; Reed, Jagust, & Coulter, 1993). Equally, measures of executive function sometimes show a relationship with awareness (Auchus, Goldstein, Green, & Green, 1994; Lopez et al., 1994; Mangone et al., 1991; Michon, Deweer, Pillon, Agid, & Dubois, 1994; Starkstein, Fedoroff, Price, Leiguarda, & Robinson, 1993), though many studies, using large sample sizes, have also failed to show this relationship (Derouesné et al., 1999; Hannesdottir & Morris, 2007). The degree of memory impairment has, on the whole, not been related to a lack of awareness (Correa, Graves, & Costa, 1996; Debettignies et al., 1990; Derouesné et al., 1999; McGlynn & Kaszniak, 1991; Michon et al., 1994; Reed et al., 1993). Other, less consistent correlates include affective variables, with anxiety and some, possibly milder aspects of depression, showing an association with increased self-awareness (Aalten, Van Valen, Clare, Kenny, & Verhey, 2005). On the whole, the literature shows great variability of awareness among dementia patients, possibly due to heterogeneity of dementia severity and measures employed. Also, different types of dementias may present with distinct impairment and awareness profiles (O'Keeffe, Murray et al., 2007). In a study by Kashiwa et al (2005), inhibitory abilities on the Stroop task were also shown to relate to level of self-awareness.

Disordered awareness may also be a feature of other neurological illnesses, such as Huntington's Disease (HD) and Parkinson's Disease (PD), two degenerative conditions characterised by impaired movement control and cognitive decline. HD and PD patients' awareness of their involuntary movements has only been investigated in very few studies, and results suggest that they may experience profound unawareness of both motor and cognitive symptoms (Shenker, Wylie, Fuchs, Manning, & Heilman, 2004; Snowden, Craufurd, Griffiths, & Neary, 1998; Vitale et al., 2001). This unawareness may be related to disease severity among HD patients (Vitale et al., 2001), though more studies are required to confirm this finding. Awareness of cognitive ability may also be impaired among patients with Corticobasal Degeneration (CBD) and Progressive Supranuclear Palsy (PSP), two atypical sporadic movement disorders which are frequently misdiagnosed as PD (Litvan et al., 2003). This was examined in one study to date, where metacognitive knowledge and the ability to predict cognitive performance were significantly impaired for both CBD and PSP patients (O'Keeffe, Murray et al., 2007).

Among acute stroke patients, notably those who have suffered predominantly right brain damage, estimated incidence rates of self-awareness deficits are variable, ranging from 7% (Jehkonen, Ahonen, Dastidar, Laippala, & Vilkki, 2000), to as high as 50-60% (Cutting, 1978) or even 80% (Marcel et al., 2004). Many investigators have commented on fact that frank unawareness in acute cases undergoes change over time, and may 'dissolve' into different syndromes (e.g. Prigatano, 2003). The time course and characteristics of these changes are poorly understood, however (Levine, Calvanio, & Rinn, 1991). In a recent investigation of other clinical correlates of anosognosia among stroke patients

with right brain damage, Baier & Karnath (2008) showed that up to 92% of patients who were unaware of their motor deficit also exhibited an abnormal sensation of body ownership for their dysfunctional limb. Other studies have shown that patients, rather than moving the plegic arm when requested, may simply insist that they have performed the required movement, a phenomenon which has sometimes been considered a specific type of confabulation (e.g. Feinberg, Roane, & Ali, 2000; Levine et al., 1991). Finally, unawareness syndromes following right hemisphere stroke are often accompanied by symptoms of unilateral neglect (e.g. Appelros, Karlsson, Seiger, & Nydevik, 2002; Berti et al., 2005), which has led to the suggestion of an underlying core deficit in motor and space representation among these stroke patients (Berti et al., 2005; Rizzolatti, Fadiga, Gallese, & Fogassi, 1996). However, anosognosia for motor plegia and unilateral neglect have also been found shown to be doubly-dissociated, and may perhaps best be understood as functionally independent disorders (e.g. Orfei, Robinson, Prigatano et al., 2007).

Relatively little is known about the characteristics of unawareness among aphasic patients, although individual case studies suggest that patients with jargon aphasia in particular may show profoundly impaired awareness of their deficit (e.g. Rubens & Gerrit, 1991). These patients frequently show no evidence of recognizing or correcting their speech errors when they occur, however, in some cases are able to recognize errors in recordings of their speech (Shuren, Hammond, Maher, Rothi, & Heilman, 1995). Systematic studies of unawareness of language dysfunction are complicated by the fact that many tests of self-awareness are themselves verbal in nature, and thus rely

on unimpaired linguistic function. Two notable features have emerged, however:

1) Some patients may show selective awareness for some aspects of their linguistic function, for example errors in one output modality, but not for others (Rubens & Gerrit, 1991), suggesting specificity of unawareness; and

2) a reduced attentional capacity may account for the observed speech errors and patients' inability to monitor and correct them (Maher, Rothi, & Heilman, 1994; Shuren et al., 1995).

In summary, although findings are often difficult to integrate due to methodological differences, it appears that across diverse patient groups, executive, memory and attentional functions appear to play an important role in accurate self-awareness. Furthermore, the use of diverse measures of executive function most likely accounts for slight inconsistencies across studies, since the executive functions incorporate multiple dimensions (Varney & Stewart, 2004). The link to executive functions does, however, point to the potential importance of frontal lobe functioning for accurate self-awareness. The following section will provide an overview of the neuroanatomical correlates of self-awareness which have been reported in the literature.

1.5 Neuroanatomical Areas Implicated in Self-Awareness

Knowledge of the putative neuroanatomic substrate that gives rise to self-awareness comes from two sources: the study of lesioned structures in neurological patients who display altered self-awareness on the one hand, and – more recently – the analysis of activation patterns observed during functional neuroimaging paradigms. Both methods have drawbacks: individual neurological patients may present with unique clinical profiles, making it difficult to deduce generalizable principles. Neuroimaging findings, in contrast, due to their correlational nature, cannot pinpoint whether individual activations are causally involved or epiphenomenal (Fellows et al., 2005). This section will review neuroanatomical findings from patient studies first, and subsequently evaluate the contribution of fMRI studies to this field.

Since the earliest observations of impaired self-awareness in clinical patient groups, there has been inconsistency in reports concerning the association between anatomical areas and subsequent unawareness. Unawareness was described both in cases of right hemisphere and left hemisphere damage, though notably more frequently following right-sided injury (see McGlynn & Schacter, 1989, for a review), although it must be borne in mind that autopsy procedures were limited in some early cases. Since the development of improved imaging procedures for visualization and measurement of cerebral damage during the 1980s and 1990s, accuracy of lesion characterisation has improved vastly (Carter & Pretorius, 2007). This has lead to some attempts to quantify the many aspects of neural damage associated with TBI, and link them to unawareness symptoms. Using such an approach, Cicerone & Tanenbaum

(1997) report on a TBI patient with orbitomedial frontal lobe damage, who showed poor awareness of her impaired social cognition. Ranseen, Bohaska, & Schmitt (1990) demonstrated that those TBI patients who showed predominantly right-lateralized lesions on CT had significantly larger questionnaire discrepancies than those with left-lateralized or bilateral injury. Other TBI studies, in contrast, have failed to show a consistent relationship between lesion location or lesion volume and unawareness, and have instead stressed the importance of lesion *number* in predicting unawareness symptoms (Prigatano & Altman, 1990; Sherer, Hart, Whyte, Nick, & Yablon, 2005).

Miller et al. (2001) used Single Photon Emission Computed Tomography (SPECT) to show that hypoperfusion or atrophy of the right frontal lobe was associated with a "loss of self" in six out of seven patients with Frontotemporal Dementia (FTD). While this study did not evaluate self-*awareness* directly, the findings suggest that the disruption of specific pathways may contribute to the impairments seen in FTD patients, of which the loss of insight is a core feature (Neary et al., 1998). Furthermore, SPECT measures of hypoperfusion in AD have also implicated similar regions, including right dorsolateral prefrontal cortex (DLPFC) and right inferior frontal gyrus, in impaired self-awareness (Reed et al., 1993; Starkstein et al., 1995; Vogel, Hasselbalch, Gade, Ziebell, & Waldemar, 2005). Hanyu et al. (2008) have shown that significant differences between aware and unaware AD patients existed in terms of perfusion of the right subcallosal, anterior cingulate and cingulate gyri and left orbital, subcallosal, and anterior cingulate gyri, implicating a bilateral frontal network for awareness among these patients.

Few studies have investigated the neuroanatomical underpinnings of unawareness among schizophrenia patients. Among those that have, many have focused on measures of brain volume, such as ventricle-brain ratio, but no clear relationship emerged (e.g. David et al., 1995). Four studies have attempted to provide morphometric measures of specific cortical areas. The first of these showed abnormal gyrification in right frontal cortex among a sample of male schizophrenic subjects, established at post-mortem (Vogeley et al., 2000). This finding was later replicated in vivo using MRI (Vogeley et al., 2001). Using measures if cortical volume, Flashman et al. (2001), showed decreased middle frontal gyrus, gyrus rectus, and left anterior cingulate gyrus volumes in schizophrenia patients compared to controls. Finally, Shad, Muddasani, Prasad, Sweeney, & Keshavan (2004) reported decreased volume in right DLPFC among those schizophrenic patients who had poor awareness of symptoms.

The findings from these three patient studies – TBI, the cortical dementias and schizophrenia – must be interpreted cautiously. As highlighted previously, both CT and MR frequently under-estimate the extent of diffuse injury in TBI patients (e.g. Huisman et al., 2004), therefore limited conclusions can be drawn from these TBI studies. Similarly, multiple networks become dysfunctional in degenerative disorders such as AD and FTD (Knowles et al., 1999). Among studies of schizophrenia patients, considerable variability may exist for factors such as long-term medication use and onset of symptoms, therefore more systematic studies are required to corroborate reports of volume reduction in bilateral or right frontal lobe regions.

Patients with relatively focal neural injury, as for example due to stroke, may provide more informative insights into the neuroanatomical nature of self-awareness. Pia, Neppi-Modona, Ricci, & Berti's (2004) meta-analysis of studies published between 1938 and 2001 demonstrated that although much variation exists between studies, unawareness of plegia occurs most frequently when a combination of right frontal and parietal structures is damaged by stroke. In a series of studies examining anosognosia among right-lateralized stroke patients, Baier and colleagues (Baier & Karnath, 2008; Karnath, Baier, & Nagele, 2005) have shown the importance of the right posterior insula for awareness of hemiplegia. In a further effort to disentangle the effects of right frontal and right parietal injury on motor function and motor awareness, Arzy, Overney, Landis, & Blanke (2006) presented a single case study of a patient with asomatognosia – an abnormal belief that one's limb has disappeared – whose neuropathology was confined to the right pre-motor and motor cortex, supporting a specific role for right frontal lobe cortices for awareness. This is further supported by a single case study of persistent anosognosia in a patient with haemorrhagic stroke affecting right parietotemporal cortex, where SPECT measures showed additional right DLPFC and ventral cortex hypoperfusion (Venneri & Shanks, 2004). In a large group of acute stroke patients, Starkstein et al. (1992) showed that those patients classified as "anosognosic" had a higher frequency of right thalamic, as well as right temporoparietal cortical lesions. Furthermore, subcortical lesions were found to be important, as anosognosia was also associated with basal ganglia lesions and bilateral frontal subcortical atrophy (prior to stroke). The authors speculate that the presence of frontal and diencephalic atrophy may be a predisposing factor for the development of anosognosia following right hemispheric lesions. Other case

studies have shown unawareness for motor dysfunction following left or right–lateralised infarction of the brain stem, specifically the pontine region (Bakchine, Crassard, & Seilhan, 1997; Evyapan & Kumral, 1999), which projects directly to the limbic system and thalamus, and indirectly to parietofrontal cortices, and therefore may contribute to dysfunction in a frontoparietal network mediating self-awareness. Similarly, House & Hodges (1988) and Ellis & Small (1997) have emphasized the role of deep white matter and basal ganglia lesions in disrupting frontal systems connectivity, and thereby contributing to self-awareness impairments. Lastly, in a large study of 140 patients with focal unilateral frontal lobe tumours, right frontal lobe tumours were reported as significantly associated with under-estimation of cognitive symptoms (Belyi, 1987).

The majority of the findings presented so far appear to suggest asymmetric hemispheric contributions to deficit awareness. However, a significant limitation of group studies examining self-awareness deficits among patients with focal neural injury, as for example caused by stroke or tumour, is the lack of a suitable clinical control group. Many stroke studies focus quite specifically on right hemisphere lesion patients, and either exclude those with left brain damage intentionally (e.g. Bisiach, Vallar, Perani, Papagno, & Berti, 1986; Jehkonen et al., 2000) or by using exclusion criteria which essentially eliminate left brain damage, such as presence of linguistic deficits in acute stroke (e. g. Starkstein et al., 1992). Additional insights into the neuroanatomical nature of self-awareness may be gained from studies using the Wada procedure, during which patients undergo pre-surgical inactivation of one hemisphere at a time by means of intracarotid barbiturate injection. Numerous studies of this type

have shown that unawareness of motor dysfunction occurs more frequently following right hemisphere inactivation (Adair, Gilmore, Fennell, Gold, & Heilman, 1995; Breier et al., 1995; Carpenter et al., 1995; Gilmore, Heilman, Schmidt, Fennell, & Quisling, 1992; Lu et al., 1997), with related symptoms of disordered awareness such as asomatognosia and phantom limb perception also showing specific right hemisphere effects (Lu et al., 2000; Meador, Loring, Feinberg, Lee, & Nichols, 2000). In addition, Keenan et al. (2001) have demonstrated that right hemisphere inactivation during the Wada procedure significantly interferes with the ability to recognize one's own face. In contrast, Dywan, McGlone, & Fox (1995) report that unawareness was equally frequently observed following left or right-sided inactivation, and was related to the functioning of the temporal lobe during the Wada test, rather than degree of laterality or frontal lobe functioning.

FMRI studies have examined patterns of neural activation during tasks that specifically involve self-related processing, including self-face recognition, 'self' – 'other' judgments and theory-of-mind abilities. Conditions requiring these functions are presumed to involve self-awareness processes, albeit to varying degrees (see also Morin, 2007). Such studies have revealed regional activations which are remarkably similar to those areas implicated by patient studies, including medial prefrontal cortex (Gusnard, Akbudak, Shulman, & Raichle, 2001; Johnson et al., 2002; Kelley et al., 2002; Macrae, Moran, Heatherton, Banfield, & Kelley, 2004; Platek et al., 2004), thalamus (Johnson et al., 2002) and right prefrontal cortex (Uddin, Kaplan, Molnar-Szakacs, Zaidel, & Iacoboni, 2005; Vogeley et al., 2001). Kjaer, Lou and colleagues used PET to measure regional blood flow while participants intensely reflected

upon their own personality traits, or those of somebody else (Kjaer, Nowak, & Lou, 2002; Lou et al., 2004). Self-reflection was associated with blood flow in functionally connected areas along a frontoparietal midline, including the precuneus and angular gyrus. Activation of more posterior areas has also been shown in other studies, such as the right temporoparietal junction and right inferior parietal lobule (Uddin et al., 2005; Vogeley et al., 2001). More recently, Farrer et al. (2008) have again shown the importance of parietal cortex, specifically the angular gyrus, for representing action awareness among healthy individuals.

A number of studies have also highlighted the potential role of the anterior insula for interoceptive processing and human awareness (e.g. see Craik, 2004, for a review). Interestingly, the lateralized effects have been reported here, too: Critchley and colleagues have reported that activation in right anterior insula cortex may be directly related to participants' awareness of bodily feelings and emotionality (Critchley, Wiens, Rotshtein, Öhman & Dolan, 2004). These findings are yet to be complemented by studies of patients with selective lesions to the anterior insula, however, they point to a prominent role for this structure within a potential larger-scale network mediating human subjective experience. This hypothesis has been explored further in models of subjective awareness such as that of Damasio, as discussed in Section 1.6 below.

While the neuroimaging studies show remarkable overlap with each other and the clinical lesion studies described above, a number of studies also exist which show no such agreement. Intentional and incidental self-reflection were both associated with left superior parietal cortex activation in Kircher et al.'s (2002)

fMRI study, while specifically *intentional* self-reflection activated the left precuneus. Klein et al. (2007) used an error monitoring paradigm which allowed aware antisaccade errors to be analysed separately from unaware errors, and showed that aware errors were associated with increased activity in the left anterior inferior insula. Similarly, Hester, Foxe, Molholm, Shpaner, & Garavan (2005) trained participants to indicate awareness of no-go commission errors, and this led to increases in bilateral frontal and parietal activation.

In summary, there are a number of neuroimaging studies which corroborate findings from patient studies, in that they commonly, though not always, implicate frontal systems and right-lateralised parietal regions for self-awareness. As previously mentioned, however, the correlational nature of neuroimaging experiments cannot inform us about the causative role of these regions. Studies of patients with specific neural damage, where a circumscribed part of a well-characterised network is non-functional, may provide more informative results. Patients with such lesions are rare, however, and additionally, it must be borne in mind that functional re-organisation may occur following injury. A suitable compromise may be a combination of functional neuroimaging techniques with patient studies, such that areas of activation can be shown when a network is already damaged. Such studies are slowly increasing in number, as neuroimaging systems become more commercially viable. Using such an approach, Ries et al. (2007) showed that participants diagnosed with mild cognitive impairment – a group at high risk for developing AD – showed attenuated activation of the cortical midline structures typically observed during self-processing. Additionally, the degree of unawareness of cognitive function emerged as a significant predictor of cortical midline

activation. Schmitz, Rowley, Kawahara, & Johnson (2006) used a self-appraisal task during fMRI scan which showed that both TBI patients and controls activated medial prefrontal areas during self-referential processing. Furthermore, decreased activation in right anterior dorsal PFC was significantly associated with decreased self-awareness among TBI patients.

In conclusion, the studies outlined above have pointed to the importance of a network of regions, including frontal cortical systems, midline structures, and parietal cortices, with particular emphasis on the importance of the right hemisphere for self-awareness processes. While the notion that a unique brain centre can be responsible for self-awareness computations is too simplistic, a basis is nonetheless provided for postulating that some neuroanatomical areas play a more important role than others, and for the purpose of the present dissertation, the role of right prefrontal cortex is of particular relevance. The following section will review theoretical accounts of self-awareness impairments, with a specific emphasis on neuroanatomical, neurocognitive and functional models.

1.6 Theoretical Models of Self-Awareness

1.6.1 Neuroanatomical Models

A number of models have been proposed which attempt to account for the neurobiological findings of disordered self-awareness cited above. For the purpose of the present dissertation, the most important views are those which focus on two neuroanatomical aspects: the frequent involvement of right hemisphere structures, and frontal lobe regions, in their capacity as supramodal executive control systems (Shallice, 1988).

All right-hemisphere models of self-awareness assume that the properties of right-lateralized structures differ fundamentally from those on the left, in a manner that gives them a biologically plausible advantage for processing self-related material. Friedlander (1964) suggested an explanation based on handedness and hemispheric dominance, in that the non-dominant hand (i.e. left hand) would be used less frequently and with less precision than the right hand. He further suggested that the right hemisphere therefore contained smaller motor and somatosensory representations than the left, and if these small representations were damaged, the percept for the contralateral side of the body would be lost. Patients with right-sided lesions would be more vulnerable to such a loss of percept, since smaller injuries were sufficient to cause unawareness of motor disorder. Left-sided injuries, on the other hand, would only lead to a lack of awareness in cases with large tissue damage, which could account for the fact that unawareness had occasionally been

observed following left hemisphere lesions (McGlynn & Schacter, 1989). More recent models would consider unawareness to be primarily a result of right-hemisphere damage because of a right-brain advantage for correlating multisensory stimuli in an effort to create a continually flowing sense of bodily unity (e.g. Haggard, Taylor-Clarke, & Kennett, 2003), a view which was shared by Critchley (1953). A contrasting explanation was proposed by Geschwind (1965), who suggested that anosognosia for hemiplegia was caused by a disconnection of the right-hemisphere regions from left-hemispheric cortical speech centres. This would occasionally cause patients to confabulate regarding the state of their affected limb.

Many early theoretical explanations were developed in order to account for the specific deficits observed in patients who were unaware of left-sided hemiplegia (McGlynn & Schacter, 1989; Orfei, Robinson, Prigatano et al., 2007). Although Friedlander's handedness hypothesis paved the way for considerations of the importance of body representation, it is now known that symptoms of a disordered body schema may occur independently of unawareness of hemiplegia (Spinazzola, Pia, Folegatti, Marchetti, & Berti, 2008), thus the mechanisms involved in these phenomena must differ at some level. Geschwind's disconnection hypothesis, although emphasising the importance of functionally connected, distributed networks, provides no explanation as to why patients fail to communicate non-verbally about the nature of their deficit.

More recent models have focused on a number of other functions for which the right hemisphere may show preferential processing, including emotional

function (Gainotti, 1997; Meador et al., 2000), intention (Heilman, 1991; Heilman & Valenstein, 1979), motor and space representation (Berti et al., 2005; Lu et al., 2000; Rizzolatti et al., 1996) and attention and arousal (Starkstein et al., 1992). Emphasising these functions is essentially an attempt to incorporate the diverse symptoms which have been observed, primarily among patients who show unawareness during acute stages of illness. The idea that malfunctioning of any of these processes plays a causal role for unawareness has been taken up in Damasio's model, which views consciousness as a high-order operation among a continuum of states, beginning with a bodily "proto-self" and extending through "core consciousness" into "extended consciousness" (Damasio, 1999). Anosognosia for motor dysfunction, in this model, is considered a hybrid disorder, caused by an anomalous extended consciousness and partially defective proto-self, for which the right hemisphere is crucial, as it contains the tools for emotional, intentional, motor, spatial, attentional and arousal processing.

Again, however, profound unawareness, for example of cognitive symptoms, may occur in the absence of emotional, intention, spatial or attentional dysfunction (Orfei, Robinson, Bria, Caltagirone, & Spalletta, 2007; Prigatano, 2003), therefore the models which base awareness impairment primarily on these processes remain limited. Instead, Stuss and colleagues (Stuss, 1991; Stuss & Benson, 1986) proposed a model which emphasized the role of the frontal lobes, as mediators of self-awareness at the top of a hierarchy of brain functions, including visuospatial, language, memory etc. The model suggests that lesions to posterior areas may produce focal disturbances of awareness, depending on specific lesion location. Direct damage to frontal systems,

however, would produce a dissociation of knowledge from the capacity to self-reflect. This hypothesis has been elaborated more recently, to include the suggestion that the frontal lobes allow our capacity for "autonoetic consciousness" – the ability to experience and re-experience episodic events and tie these events to our selves as the owner of these experiences (Wheeler, Stuss, & Tulving, 1997; Stuss et al, 2001).

Other models of human functional neuroanatomy have also shared this view of frontal lobe structures as the seat of supervisory control systems, orchestrating individual sub-ordinate processes (e.g. Goldberg & Bilder, 1987; Shallice, 1988). Neurobiologically, this is an appealing theory, for two reasons: 1) The frontal lobes – in particular the prefrontal cortices (PFC) - are reciprocally interconnected with virtually all other areas of the nervous system, placing them in an ideal position for monitoring other systems (Pandya & Barnes, 1987); and 2) Single neurons within prefrontal cortex are uniquely flexible, can code abstract rules, and are able to aid in the creation of abstract representations of ourselves in space and time (e.g. Rougier, Noelle, Braver, Cohen, & O'Reilly, 2005; Wallis, Anderson, & Miller, 2001). Additionally, recent evidence has suggested that even specific unawareness of motor impairment is frequently associated with frontal lobe damage, in addition to right parietal injury (Pia et al., 2004). Right frontal areas have furthermore been implicated for episodic memory retrieval in PET and fMRI studies, lending further support to the "autonoetic consciousness" hypothesis (Cabeza & Nyberg, 2000).

Figure 1.1 shows a schematic of some of the interconnections of the PFC, as simplified by Miller & Cohen (2001), illustrating the immense connectivity of the frontal lobes.

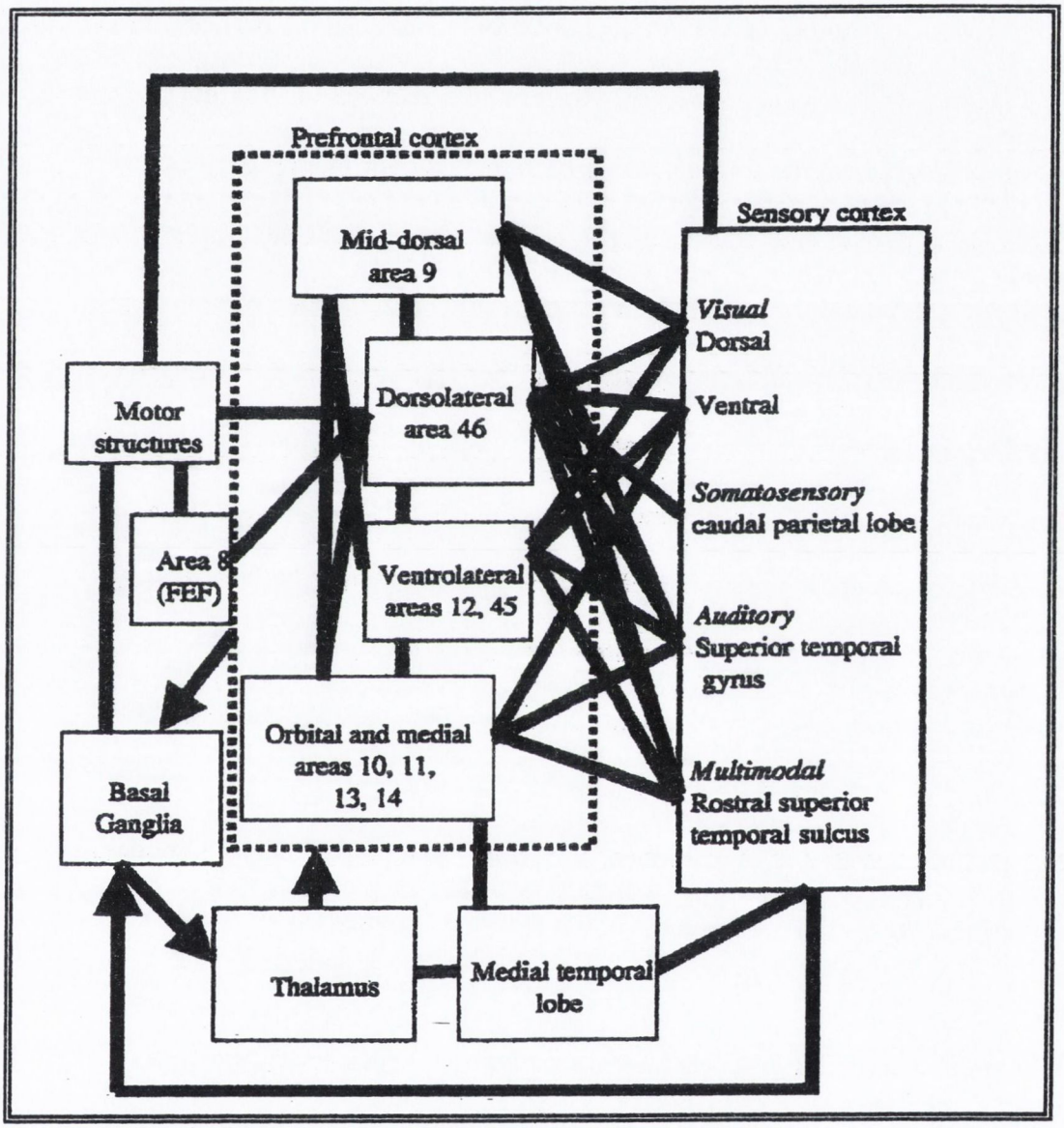


Figure 1.1. Simplified Schematic of PFC Connections. All connections are reciprocal, except those indicated by arrow. The frontal lobes are in a unique position to monitor functional sub-systems, and create a sense of self-awareness by linking the output of these systems to 'self'. From Miller & Cohen (2001).

Other authors have criticised the hierarchical structure of the frontal lobe model, and have instead suggested the existence of functionally different disorders of self-awareness, resulting from injury to frontal, parietal, temporal or occipital heteromodal association cortex, respectively (Prigatano, 1991; 1999), based on Mesulam's (1985) subdivision of association cortices into "unimodal" and "heteromodal" areas. Heteromodal cortices include not only PFC, but also areas of the inferior parietal lobule, superior marginal gyrus and angular gyrus. This model further suggests that only bilateral damage would lead to complete unawareness syndromes, while unilateral damage would cause partial syndromes. One advantage of such a view is it attempts to account for many diverse clinical and neuroanatomical findings, including those pertaining to unawareness of cortical blindness, where bilateral occipital damage is common (Bisiach & Geminiani, 1991). Large networks involving heteromodal cortices would appear uniquely suited for integrating information relevant to the external world and the internal milieu, thus be strong candidates for integrating thinking and feeling, to produce self-awareness. Although primarily developed to account for impaired self-awareness in TBI patients, this model could also be applied to unawareness in other clinical groups.

In summary, a number of models have been proposed which focus primarily on the underlying neuroanatomical substrate, in an attempt to account for the diverse clinical neuropsychological findings reported throughout the literature. While earlier hypotheses were not able to account for the many, often subtle symptoms of the disorder, some of the more recent models are flexible enough to incorporate contemporary neuroscience themes – for example the question of the functional neuroanatomy of human PFC – and thus have the potential to

be adapted and extended further, as our knowledge of the neurobiological properties of the relevant structures increases.

1.6.2 Neurocognitive Models

One of the earliest and most influential neurocognitive model proposed to account for impaired self-awareness observed among neurological patients was the Dissociable Interactions and Conscious Experience (DICE) model (McGlynn & Schacter, 1989; Schacter, 1990). The model postulates a cognitive structure known as the "conscious awareness system", involving the inferior parietal lobes and cingulate area, which, if disconnected from other cognitive modules, would give rise to unawareness of specific deficits. Damage to the conscious awareness system itself would give rise to "unawareness of all neuropsychological deficits that occur in a particular patient" (McGlynn & Schacter, 1989, p.190).

Agnew & Morris (1998) further developed the DICE model to account for self-awareness deficit among AD patients, emphasising the link between a "personal database" which must be updated, and the experience of task performance. A number of comparator mechanisms within the "central executive system" detect mismatch between actual and expected performance, and signal this mismatch to the "metacognitive awareness system" (Morris & Hannesdottir, 2004). "Primary anosognosia" would thus arise from failure of the metacognitive awareness system. "Secondary anosognosia" can further be

subdivided into "mnemonic anosognosia", which would result from memory failure itself leading to a failure to update the personal database, and "executive anosognosia", which would result from malfunctioning of the comparator mechanisms (Hannesdottir & Morris, 2007). Importantly, primary and mnemonic anosognosia would allow for a level of implicit awareness to remain, so that some degree of behavioural adaptation can be observed. Only when comparator mechanisms have been rendered dysfunctional, both explicit and implicit awareness fails. The model therefore has merit for clinical settings, where implicit awareness can sometimes be inferred in patients (Ownsworth, Clare, & Morris, 2006). Individual forms of unawareness described in this model remain to be experimentally investigated, particular in patient groups other than AD (Ansell & Bucks, 2006).

1.6.3 Functional Models

Functional models have been developed in order to provide clinicians and rehabilitation professionals with useful conceptual frameworks within which to locate individual patients' performance and functional progress. Additionally, they attempt to draw together a range of diverse findings regarding the specificity of unawareness symptoms, which cannot be adequately captured by most neuroanatomical models. A number of investigators have noted that many factors other than the underlying neuropathology influence unawareness, such as the "object of insight" that is assessed (Markova & Berrios, 2001), the specific assessment method (e.g. Marcel et al., 2004), personality factors

(Prigatano, 1996b) and the social environment in which the behaviours in question are elicited and interpreted (e.g. Clare, 2003). Many of these factors have been integrated in biopsychosocial models of self-awareness, such as that of Ownsworth et al. (2006), which have great applicability to rehabilitation settings. This review, however, for the sake of the current dissertation, will focus on those models which have drawn theoretical distinctions between different functional *types* of self-awareness.

Crosson et al. (1989) proposed a model of this type, which described self-awareness in terms of a three-tiered hierarchical structure, comprised of "intellectual awareness" (basic knowledge about having an impairment), "emergent awareness" (the capacity to recognize a problem when it occurs) and "anticipatory awareness" (the ability to anticipate future consequences of the impairment). Also referred to as the Pyramid Model, these levels were originally described in order to account for the re-emergence of self-awareness following TBI. The main emphasis, therefore, is on the interdependence of these three levels, such that intellectual awareness provides the foundation for emergent awareness, which in turn is a prerequisite for anticipatory awareness. Evidence for a hierarchy among such types of awareness has been lacking (e.g. Abreu et al., 2001), leading to a criticism of the rigid structure of such a model. Instead, Toglia & Kirk (2000) developed the pyramid model further, incorporating a range of clinical and experimental findings across many patient groups, as summarised in their Comprehensive Dynamic Interactional Model (CDIM). According to this view, self-awareness should best be considered as comprised of "metacognitive knowledge", which exists prior to task begin, and "online awareness", which is situational and dynamically influences

metacognitive knowledge. Metacognitive knowledge is seen here as a broader concept than intellectual awareness, in that knowledge about the task required, as well as self-beliefs, are included in this category. Equally, online awareness essentially includes emergent awareness during tasks and the ability to anticipate performance, though no hierarchy between these functions is specified.

These models are useful in that they can flexibly incorporate the diverse factors which have been found to impact on self-awareness measurements, and furthermore, they are of help to clinicians in that predictions are made about what to expect when patients perform tasks that tap into the domains specified. Experimentally, both the Pyramid Model and the DCIM allow for the development of multidimensional assessment methods, which may aid in experimental attempts to capture subtle phenomena of impaired awareness.

1.7 Summary and Outline of the Present Dissertation

This review has demonstrated that self-awareness is both a theoretically challenging and clinically important topic. Although recognized since antiquity, self-awareness disturbances have only recently begun to be examined systematically, with as yet much discrepancy between clinical and experimental findings. One important source of this discrepancy is the great variation in methodologies between studies, with many reports assessing only singular aspects of self-awareness disturbances. Overwhelming evidence exists that unawareness is a multifaceted disorder (e.g. Orfei, Robinson, Bria et al., 2007; Orfei, Robinson, Prigatano et al., 2007), which calls for the development of appropriately multifaceted assessments.

The present dissertation reports findings from three studies which examine several aspects of self-awareness, among neurologically healthy participants and a large sample of patients with focal neural injury. Chapter 2 explores neuropsychological correlates of self-awareness among healthy young adults, which contributes to a much-neglected area in the self-awareness literature. The search for the neuropsychological functions which are most important for impaired self-awareness has yielded inconsistent results, as this review has demonstrated. Thus, Chapter 2 will focus those neuropsychological functions which *have* been shown to play a key role (though not consistently across patient groups), and examine them with respect to self-awareness among healthy young adults.

Section 1.5 above reviewed the findings regarding the putative neuroanatomical substrate of self-awareness deficits among neuropsychological patients. In addition, Section 1.6 has described the theoretical models which have attempted to account for those results. As shown, none of the models can readily account for all observations, however, the functional models provide a means to classify awareness into *type* of awareness which are useful for developing tasks that can measure these aspects under laboratory conditions, as in the case of online awareness. Chapter 3 therefore describes a study which investigates three types of self-awareness among right and left frontal, and right and left non-frontal focal lesion patients. Given the purported prevalence of right frontal lobe dysfunction among patients with self-awareness deficit, this study will systematically evaluate the relative contribution of right and left frontal cortex damage to impaired self-awareness, while also examining awareness among those with spared frontal control systems.

Lastly, in Chapter 4, the electrophysiological characteristics of error awareness will be investigated in a sample of frontal and non-frontal focal lesion patients, as well as a neurologically healthy control group, in the hope to elucidate the mechanisms which give rise to conscious processing of erroneous response and ultimately, accurate self-awareness. Chapter 5 will provide a summary of results, integrate findings with current models of self-awareness, and evaluate the contribution of the studies in this dissertation.

Chapter 2 : Neuropsychology of Self-Awareness in Young Adults

Abstract

Disorders of self-awareness are common following cortical damage, particularly to the frontal lobes, but there have been few studies of individual differences in self-awareness in the normal population. The current study explored patterns of metacognitive awareness among healthy young adults, based on discrepancies of self- and other-ratings on the Frontal Systems Behavior Scale (FrSBe; Grace & Malloy, 2002). Those who showed poor metacognitive awareness showed more frequent lapses of attention, and higher levels of everyday absentmindedness, than those who accurately appraised their own behavior or those who over-estimated their own FrSBe scores. Furthermore, among those with poor metacognitive awareness, online emergent awareness correlated positively with prospective memory performance, and negatively with anxiety scores. These results suggest that accurate self-awareness in non-neurological participants relies on efficient sustained attention functioning, supporting the role of frontal control systems in neuroanatomical models of self-awareness.

2.1 Introduction

As discussed previously, self-awareness can be defined as the accuracy of individuals' assessments of their past, current or future behavior, measured either in relation to objective performance, or in relation to the ratings of significant others or caregivers. Self-awareness/insight is of considerable importance in brain rehabilitation since a lack of acknowledgement of problems mitigates against taking the necessary steps to overcome them, as many studies have documented (Fleming et al., 1996; Sherer, Bergloff et al., 1998).

As discussed in Chapter 1, disorders of self-awareness are common following cortical damage (O'Keeffe, Dockree et al., 2007; O'Keeffe, Murray et al., 2007; Prigatano & Schacter, 1991), and particularly to the frontal lobes (McDaniel, Edland, & Heyman, 1995; Stuss, et al., 2001). However, the previous chapter has also shown that impaired self-awareness can be observed after damage to many diverse regions, including right parietal circuits (e.g., Pia et al., 2004), right insular (Karnath et al., 2005) and right pre-motor areas, such as Brodmann's areas 6 and 44 (Berti et al., 2005). While right-lateralized structures certainly appear to play an important role (Reed et al., 1993; Starkstein et al., 1992), it has been noted that compelling evidence also exists for left hemispheric involvement in self-awareness, as through the link of inner speech capacity and self-awareness (e.g., Morin & Michaud, 2007). Attempts to use CT-based lesion analyses of traumatic brain injury (TBI) patients to predict impaired self-awareness have failed to demonstrate consistent relationships between lesion location or volume and degree of

unawareness (Sherer et al., 2005). Findings from such studies must be interpreted with caution due to the diffuse nature of traumatic brain injury, making it difficult to link discrete lesions to impairment levels.

The neuropsychology of self-awareness is in itself an unresolved theoretical challenge (Prigatano, 2005). As shown in Chapter 1, attempts to understand which cognitive functions are most important for accurate self-awareness have produced mixed findings, with the most frequently-reported functions being general cognitive ability (Anderson & Tranel, 1989), memory abilities (e.g., Noe et al., 2005; Trudel et al., 1998), efficient executive functioning (Dalla Barba, Parlato, Iavarone, & Boller, 1995; Hart et al., 2005; Noe et al., 2005; Ownsworth et al., 2002; Souchay, Isingrini, Pillon, & Gil, 2003), and attentional impairments (Hjaltason, Tegner, Tham, Levander, & Ericson, 1996; McAvinue et al., 2005; O'Keeffe et al., 2007). These findings point to the importance of the efficiency of frontal lobe networks for self-awareness.

Various methods exist for assessing self-awareness, including questionnaire discrepancies between patient and "significant other" ratings (Fleming et al., 1996), a method which has the advantage of capturing awareness of naturalistic, everyday behaviors which are difficult to assess in a lab setting. The level of awareness for such behaviors will show some inter-subject variability in the general population, albeit not as extreme as in patient populations. These measures characterize individuals with respect to the background metacognitive knowledge at their disposal. In contrast, recent theoretical models distinguish such metacognitive awareness from online awareness, which includes moment-to-moment changes in self-awareness

(Crosson et al., 1989; Toglia & Kirk, 2000). Online awareness thus represents a less stable characteristic, but improvements in online detection may lead to corrective changes which could be learned and furnish metacognitive knowledge. Evidence for fractionation of unawareness as a unitary syndrome comes from patient studies reporting dissociations between awareness for different functions and deficits (e.g., Evyapan & Kumral, 1999; Jehkonen et al., 2000). Reports of patients showing awareness for impaired limb movement, but not for aphasia, for example by Breier et al. (1995), have led many investigators to call for more multifaceted assessments of disturbed awareness (e.g., Orfei, Robinson, Prigatano et al., 2007).

Little attention has been paid to self-awareness patterns in the normal population. An exception is Kruger & Dunning (1999)'s exploration of the relationship between undergraduates' level of skill and perception of competency, noting that those with low ability tended to over-estimate their performance. Though patient studies have sometimes noted substantial self-other questionnaire discrepancies among control participants (e.g., O'Keeffe, Murray et al., 2007; Rankin, Baldwin, Pace-Savitsky, Kramer, & Miller, 2005), those have not been systematically examined with respect to everyday frontal system behaviors and their neuropsychological underpinnings. The current, exploratory study aimed to investigate metacognitive awareness patterns for functions occurring along a continuum in a healthy, non-clinical sample. The Frontal Systems Behavior Scale (FrSBe) was administered to participants and their significant others, to obtain frequency ratings for behaviors typically displayed to greater extent by patients with documented damage to frontal/fronto-subcortical networks (Grace & Malloy, 2002). Here, discrepancy

between ratings from neurologically healthy individuals and their significant others were examined. Further, online awareness of errors, and its association with neuropsychological task performance, was measured. The neuropsychological battery aimed to include tasks from those neuropsychological domains with putative relationship to self-awareness, including measures of emotional, attention, memory and executive function.

2.2 Method

2.2.1 Participants

Seventy-nine young healthy participants, 35 male and 44 female, between the ages of 18 and 53 were recruited as volunteers from the Trinity College School of Psychology participant panel. Individuals who reported any of the following were excluded: loss of consciousness from a head injury, diagnosis of epilepsy or any other neurological condition, major psychiatric/psychological disorder, or history of substance abuse. All participants gave informed written consent prior to participation in the study, which was approved by the School of Psychology Research Ethics committee in Trinity College, Dublin. Seventy-one (30male, 41 female) participants and their significant others completed all questionnaires and tests, with a mean age of 22.85 years (SD 5.2), mean NART IQ = 117.27 (SD 3.3), and mean years of education = 16.05 (SD 2.1).

2.2.2 Materials and Procedure

2.2.2.1 Intellectual Functioning

Revised National Adult Reading Test (NART-R; Nelson, 1982; Nelson & Willison, 1991) as an estimate of premorbid IQ.

2.2.2.2 Emotional Functioning

Hospital Anxiety and Depression Scale (HADS; Zigmond & Snaith, 1983), which contains seven items related to levels of anxiety (e.g., "I feel tense or 'wound up'.") and seven items related to levels of depression (e.g., "I still enjoy the things I used to enjoy."), with a choice of four responses per item. Scores range from 0 to 21 for both anxiety and depression.

2.2.2.3 Neuropsychological Measures

Memory. Immediate recall of Logical Memory I, a subtest from the Wechsler Memory Scale (WMS III; Wechsler, Wycherly, Benjamin, Crawford, & Mockler, 1998). Prospective memory (Walker, 2003), a sentence verification task, (e.g. "Bishops drink tea." = true; "Dogs have wheels." = false). Embedded in the sentences was the target word "hand" which cued participants to press a nominated key. The number of key presses served as the prospective memory score.

Attention. The computerized Dual Attention to Response Task (DART; Dockree, Bellgrove et al., 2006) – participants were presented with digits 1 to 9 in sequential order on a computer screen, and required to respond to each digit by pressing the left mouse button. Additionally, participants were required to perform an embedded continuous performance task by pressing the right mouse button for grey digits in the sequence. Furthermore, participants were instructed to withhold their response to a predictable no-go target (i.e. the digit '3'). Both errors of *commission* (i.e. failure to withhold on '3') and failures of

omission during three blocks of DART were recorded. For commissions only, participants were instructed to verbally indicate their errors ('Hit') (O'Keeffe, Dockree, & Robertson, 2004). Each block consisted of 225 trials, which included 25 no-go targets and 21 grey digits. All stimuli were presented as white digits on a black background at the centre of the screen, at a distance of approximately 100cm. All digits were presented for 250ms , followed by a 900ms inter-stimulus interval (ISI). Figure 2.1 shows an example of a typical DART sequence.

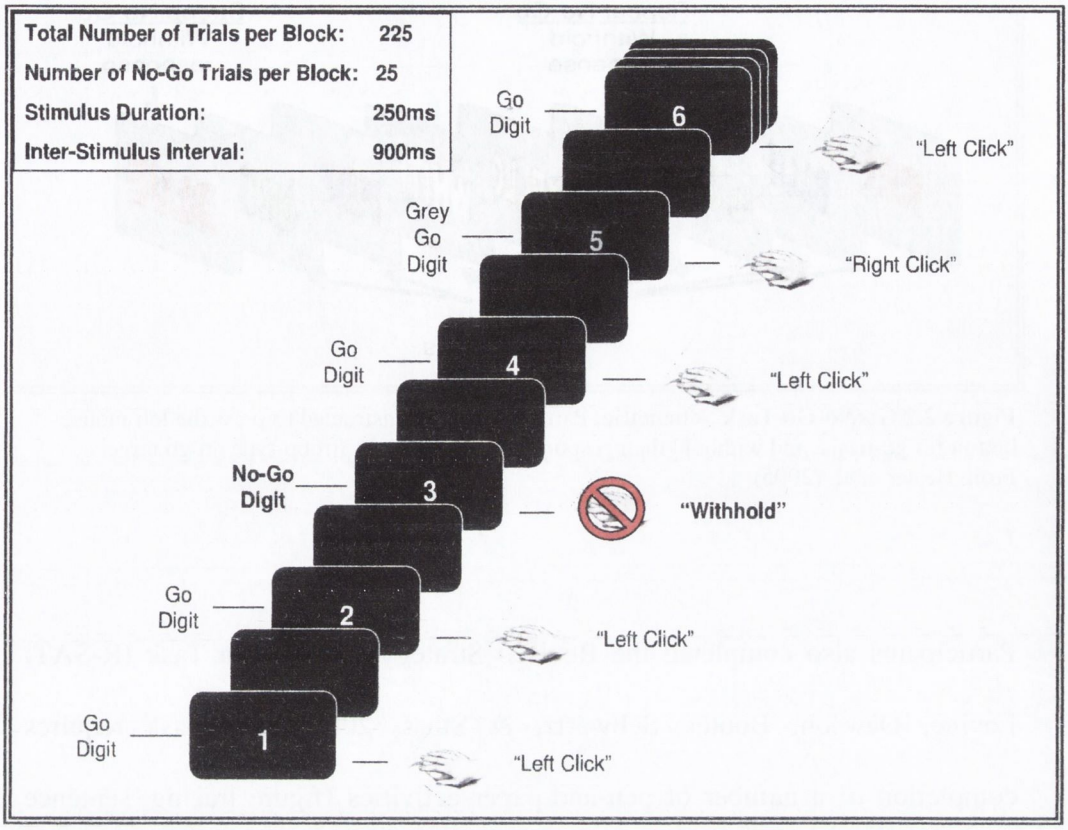


Figure 2.1. Example of a DART Sequence. Participants were instructed to left click for go digits, withhold for no-go targets, and right click for grey digits embedded in the sequence.

Executive functions. Commission errors were recorded during two blocks of a modified Stroop-based go/no-go task [originally developed as the Error Awareness Task (EAT); Hester et al., 2005], during which participants were presented with frequent go-trials (congruent colour words) and infrequent no-go targets (repeated or Stroop-type colour words). Go-trials required a left mouse button response, while no-go targets required participants to withhold button press. Each block included 200 go-trials and 25 randomly interspersed no-go trials. Stimuli were presented for 600ms, with an ISI of 900ms. Figure 2.2 shows an example of the stimuli used for the task.

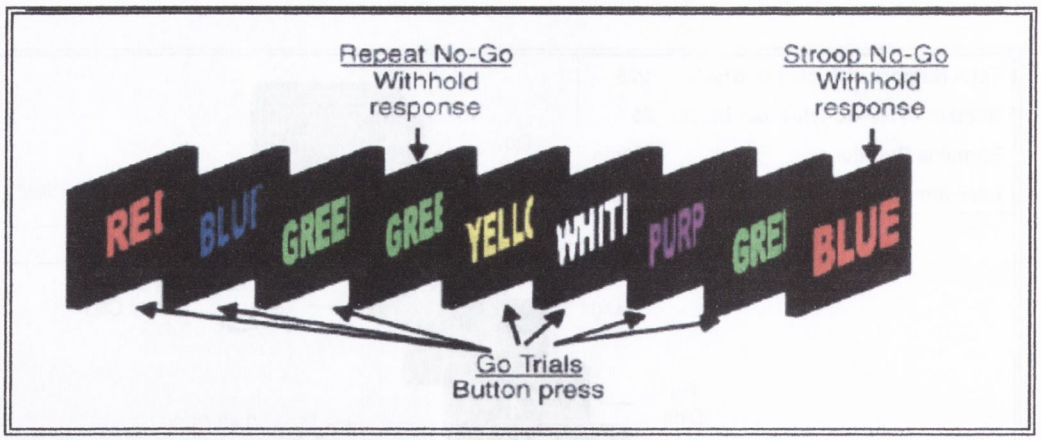


Figure 2.2 Go/No-Go Task Schematic. Participants were instructed to press the left mouse button for go-trials, and withhold their response for repeated or Stroop-type no-go targets. From Hester et al. (2005).

Participants also completed the Revised Strategy Application Task (R-SAT; Levine, Dawson, Boutet, Schwartz, & Stuss, 2000). This task requires completion of a number of pen-and-paper activities (figure tracing, sentence copying and object numbering) in the most efficient way. The primary score reflects the proportion of items completed in the most strategic manner (i.e. number of brief items completed per total number of items). Lastly, verbal fluency was measured and defined as the total number of words participants were able to generate during 60 seconds for the letters F, A & S (Spreen & Strauss, 1998).

2.2.2.4 Questionnaire Measures

The Frontal Systems Behavior Scale (FrSBe; Grace & Malloy, 2002) measures the frequency of symptoms typically associated with damage to frontal/fronto-subcortical brain regions, rated on 46 items ranging from "almost

never" ('1') to "almost always" ('5'). Examples of items include "Speaking only when spoken to" and "Mixing up a sequence, getting confused when doing several things in a row". The FrSBe was administered in identical form to both participants and significant others. Participants were instructed to pass 'other' questionnaires on to a family member, or alternatively, to somebody who knew the participants well and interacted with them on an everyday basis, and return completed questionnaires to the researchers.

Cognitive Failures Questionnaire (CFQ; Broadbent, Cooper, FitzGerald, & Parkes, 1982): Participants rated the frequency of absentmindedness, attentional & memory failures in everyday situations on 25 items, ranging from "never" ('0') to "very often" ('4'). Examples include items such as "Do you read something and find you haven't been thinking about it and must read it again?" and "Do you find you forget appointments?". Furthermore, a shortened version of the CFQ for Others, consisting of 8 items, was administered to participants' significant others. Examples of items include "Participant X seemed to be clumsy, for example, dropping things or bumping into people."

Measure of Empathic Tendency (MET; Mehrabian & Epstein, 1972): This self-rated questionnaire consists of 33 statements designed to measure emotional empathy. Participants indicate their agreement, ranging from "very strong agreement" (' +4') to "very strong disagreement" ('-4'), on items such as "It makes me sad to see a lonely stranger in a group", and "I become nervous if others around me seem to be nervous."

2.2.2.5 Self-Awareness Measures

2.2.2.5.1 Metacognitive Awareness

Metacognitive awareness was assessed by measuring the discrepancy between FrSBe ratings obtained from participants and significant others (self minus other).

2.2.2.5.2 Online Awareness

Online awareness was recorded as the percentage of DART commission errors verbally reported as aware during the task (O'Keeffe, Dockree, & Robertson, 2004).

2.3 Results

2.3.1 FrSBe Discrepancy Patterns

FrSBe discrepancy scores (computed as 'self' minus 'other') ranged from – 82 to + 63. Participants were divided into those with low metacognitive awareness or 'under-estimators' [(discrepancy < - 10), N = 16], accurate estimators [(discrepancy – 10 to + 10), N = 21], and over-estimators [(discrepancy > +10), N = 34] of FrSBe scores. Since a 100% agreement between participants and significant others is unlikely (even for those with close agreement), accurate estimators were defined with a small margin for error: a participant was deemed accurate if s/he disagreed by no more than *ten points*, leading to a discrepancy of plus or minus 10. Participants outside this range were classified as under-or over-estimators.

Demographic details, screening results and mean FrSBe discrepancies are shown in Table 2.1 below. Groups did not differ in terms of sex [$\chi^2 = 2.12$, df = 2, $p > 0.05$], age, years of education or NART IQ (all $F < 1$, $p > 0.05$).

Table 2.1. Participant Characteristics and Mean FrSBe Discrepancies

	FrSBe		
	Under-Estimators	**Accurate Estimators**	**Over-Estimators**
N (m, f)	16 (7, 9)	21 (8, 13)	34 (15, 19)
Age in Years (SD)	23.5 (8.0)	23.3 (6.0)	22.0 (3.0)
NART-Based IQ (SD)	117.3 (3.8)	116.9 (2.7)	117.6 (3.7)
Years of Education (SD)	15.8 (2.6)	15.6 (1.9)	16.2 (2.1)
Mean FrSBe Discrepancy (SD)	-26.00 (20.1)	3.43 (4.8)	28.94 (15.0)

Note: NART = National Adult Reading Test; FrSBe = Frontal Systems Behavior Scale

2.3.2 Neuropsychological Differences

In order to investigate differences in neuropsychological functioning between the three awareness groups, separate one-way between groups ANOVAs were performed. A main effect of group existed only for FrSBe-Self [$F(2, 68) = 7.073$, $p < 0.01$], FrSBe-Other [$F(2.68) = 12.282$, $p < 0.01$], CFQ-Self [$F(2, 68) = 3.451$, $p < 0.05$], CFQ-Other [$F(2, 68) = 6.134$, $p < 0.01$], DART commission errors [$F(2, 68) = 3.240$, $p < 0.05$], and DART omission errors [$F(2, 68) = 4.450$, $p < 0.05$]. Figures 2.3 – 2.5 display results for the posthoc Bonferroni comparisons of these effects.

In regard to reported frontal symptoms (measured by the FrSBe) an interesting pattern emerged: other-reported symptoms were significantly higher in individuals who were categorised as under-estimators compared to those who were categorised as accurate- and over-estimators (based on the

aforementioned discrepancy scores) (both $p < 0.01$). By contrast, self-reported symptoms were significantly higher for individuals who were categorised as over-estimators compared to the accurate- and under-estimators (both $p < 0.01$). The FrSBe self- and other ratings for all groups are displayed in Figure 2.3 below.

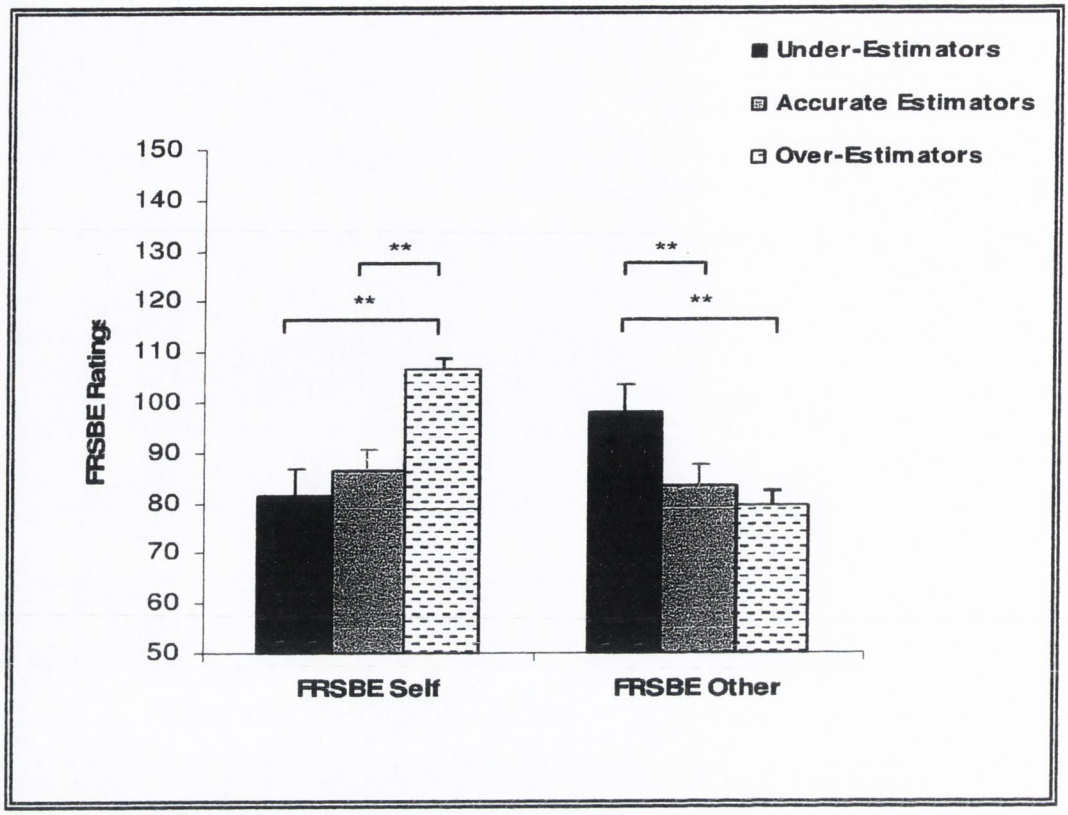


Figure 2.3. FrSBe Self – and Other Ratings as a Function of Group. Error bars represent the standard error of the mean. ** $p < 0.01$.

For CFQ ratings in our awareness groups (again based on FrSBe discrepancies), a very similar pattern was observed: Other-ratings of everyday absentmindedness were highest for the under-estimator group, compared to accurate and over-estimators (both $p < 0.01$). By contrast, self-rated absentmindedness was significantly higher among over-estimators than accurate estimators ($p < 0.05$). Figure 2.4 displays CFQ scores as a function of awareness group.

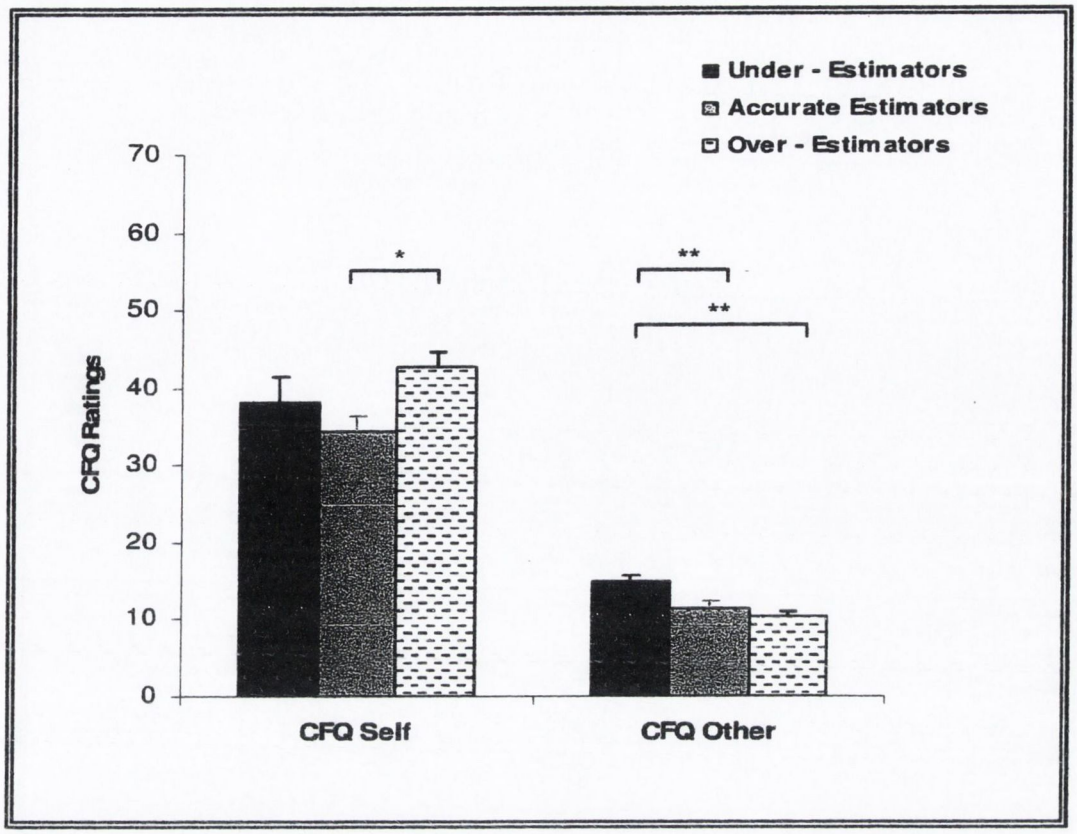


Figure 2.4. Self- and Other Ratings of the CFQ as a Function of Group. Error bars represent the standard error of the mean. * $p < 0.05$ ** $p < 0.01$

Lastly, under-estimators made significantly more DART errors of commission and errors of omission than the accurate and over-estimator group (both comparisons $p < 0.05$), as shown in Figure 2.5 below.

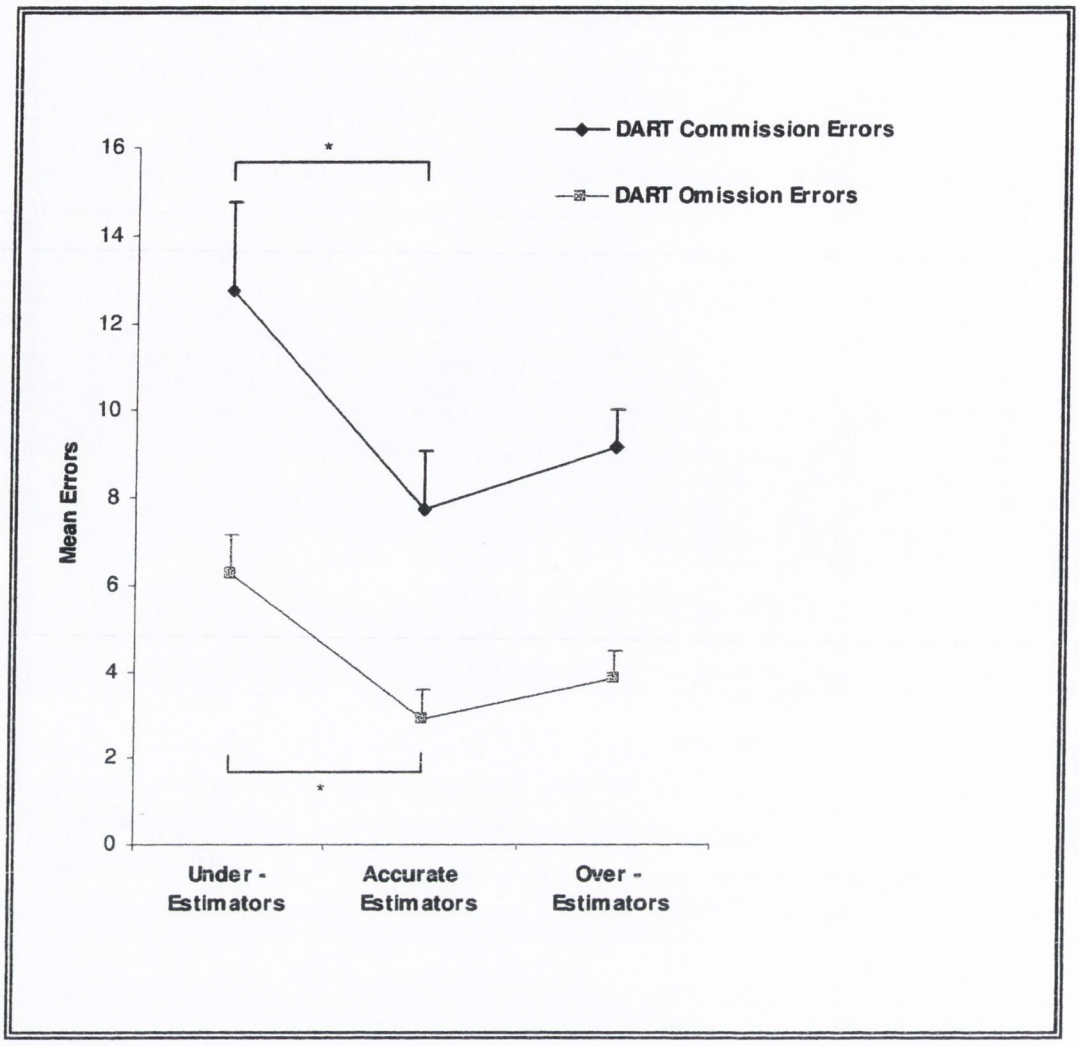


Figure 2.5. DART Errors as a Function of Group. Error bars denote the standard error of the mean. * $p < 0.05$.

No significant main effects existed for the remaining neuropsychological measures, including Logical Memory score, Prospective Memory, R-SAT, No-Go errors, FAS words, HADS scores, and MET score (all $F < 1$, $p > 0.05$). Mean scores for all measures are displayed in Table 2.2.

Table 2.2. Mean Scores on Neuropsychological Scores as a Function of Group.

	FrSBe		
	Under-Estimators	**Accurate Estimators**	**Over-Estimators**
Logical Memory (SD)	45.4 (8.5)	46.4 (7.7)	48.4 (7.2)
Prospective Memory (SD)	4.8 (1.4)	5.0 (1.4)	5.2 (1.2)
R-SAT (SD)	0.7 (0.2)	0.7 (0.2)	0.7 (0.2)
No-Go Errors (SD)	18.6 (8.9)	15.8 (8.9)	16.8 (7.4)
FAS Words (SD)	41.1 (12.4)	44.5 (14.0)	38.9 (12.7)
HADS Depression (SD)	2.8 (2.2)	3.1 (2.5)	3.5 (2.6)
HADS Anxiety (SD)	6.4 (2.8)	6.4 (2.5)	7.3 (3.2)
MET (SD)	38.3 (18.4)	31.6 (21.1)	42.9 (19.7)

Abbreviations: R-SAT = Revised Strategy Applications Task; FAS = F, A & S words generated; HADS = Hospital Anxiety and Depression Scale; MET = Measure of Empathic Tendency

2.3.3 Relationship between Emotional Functioning, Neuropsychological and Awareness Measures

In order to characterize the nature of awareness in our three groups, which showed heterogeneity with respect to neuropsychological performance, we conducted correlational analyses separately for each group. In order to reduce the number of correlations, we included only measures which have previously shown to be associated with awareness (see O'Keeffe, Dockree, et al, 2007; O'Keeffe, Murray, et al, 2007) and prospective memory, which may involve similar performance monitoring processes as other online awareness tasks. Thus our correlation matrix included HADS anxiety scores, DART

commission errors, prospective memory & metacognitive and online awareness. Since online awareness was not normally distributed (Kolmogorov-Smirnov = .163, $p < 0.05$), Spearman's rho correlations were performed. In the under-estimator group, the following relationships emerged: Higher online awareness during DART was associated with higher prospective memory scores ($r_S = .530$, $p < 0.05$), and correlated negatively with HADS anxiety scores ($r_S = -.594$, $p < 0.05$). No other significant correlations were found. The correlation matrix for under-estimators is shown in Table 2.3.

Table 2.3. Spearman's Rho Correlations for Under-Estimators

	Metacognitive Awareness	Online Awareness
HADS Anxiety	-.112	**-.594***
DART Commission Errors	-.256	-.092
Prospective Memory	-.388	**.530***

Note: * $p < 0.05$, uncorrected for multiple comparisons

2.3.4 Additional Correlational Analyses

Additional correlational analyses showed that metacognitive awareness showed no relationship with any of the neuropsychological tasks ($p > 0.05$). Equally, metacognitive and online error awareness were not significantly associated, across participants ($p > 0.05$). Lastly, the number of DART commission errors showed no relationship with online awareness of these errors ($p > 0.05$).

2.4 Discussion

This study aimed to investigate the potential neuropsychological characteristics which may underlie metacognitive awareness in the normal population. Impaired awareness of deficits is of increasing interest to professionals in clinical and rehabilitation settings, and thus often studied in clinical populations with significant cognitive and/or behavioral deficits. However, in order to fully understand the complex phenomenon of self-awareness, its correlates and mechanisms must also be understood in the normal population. The current study aimed to achieve such understanding by measuring both metacognitive and online awareness in a large sample of healthy young adults.

As a first observation, the present results show that even in non-neurological populations, it is possible to observe differences in patterns of awareness for everyday behaviors, as evidenced by the distribution of FrSBe discrepancies. Though relatively small in number, the current sample included a subset of participants who appeared to substantially under-estimate the frequency of behaviors typically associated with abnormal functioning of frontal systems. This under-estimator group, when rated by their significant others, received higher FrSBe ratings and cognitive failure (CFQ) ratings than both accurate estimators and over-estimators. By contrast, self-reported symptoms on the FrSBe were higher among over-estimators than among accurate and under-estimators. Similarly, self-reported levels of everyday absentmindedness (CFQ scores) were higher in the over-estimator than the accurate estimator group. Thus, although both the under-estimator and over-estimator group could be

viewed as showing inaccurate perceptions of their own behaviors, it is only in the *under*-estimator group that this misperception is driven by higher ratings given by a significant other, both for everyday frontal behaviors (such as dysexecutive behaviours, apathy, disinhibition) and absentmindedness.

With respect to neuropsychological functioning, lapses of sustained attention during DART, as indexed by errors of commission and omission, occurred more frequently in under-estimators than in those who accurately estimated their behavior. Previous studies have found DART commission errors to be a sensitive index of individual differences in sustained attention abilities (Dockree, Bellgrove et al., 2006), and also to accurately discriminate between Traumatic Brain Injury (TBI) patients and healthy control participants (Dockree, Bellgrove et al., 2006; O'Keeffe, Dockree, et al., 2007). Omission errors, though less frequent than commissions, also accurately discriminated between the awareness groups, suggesting that both types of errors may be useful indicators of attentional lapses.

In the under-estimator group, i.e. among those with relatively poor metacognitive awareness, online awareness showed a positive correlation with prospective memory performance. This suggests that poor error awareness and poor realization of delayed intentions may constitute closely related processes. This is supported by recent performance monitoring studies which have identified networks involved in maintaining ongoing behavior and detecting erroneous responses, such as dorsal anterior cingulate cortex/posterior medial frontal cortex (Taylor, Stern, & Gehring, 2007). It has been stressed that intact

interactions between areas such as dorsolateral prefrontal cortex and anterior cingulate cortices are crucial for efficient cognitive control (Gehring & Knight, 2000). Thus, in those participants with poor metacognitive awareness, the efficiency of such interactions may be compromised, leading to failures to maintain delayed goals and accurately detect performance errors. Though the issue of separating error detection from conscious error awareness is not fully resolved (O'Connell et al., 2007), understanding the underpinnings of local error monitoring processes may provide valuable insights into clinical unawareness phenomena (Hart et al., 1998).

Higher online awareness was also associated with lower anxiety levels in the under-estimator group. The causal relationship between emotional functioning and awareness levels remains unclear; it is conceivable that anxiety levels in the under-estimator group may have interfered with efficient performance monitoring. Alternatively, anxiety may be a consequence of persistent negative events that poorer error monitoring gives rise to. It has previously been reported that decreased online awareness of errors is associated with increased anxiety levels in TBI patients (O'Keeffe, Dockree et al., 2007). Furthermore, metacognitive awareness has sometimes, but not consistently, been related to anxiety levels (e.g. Aalten et al., 2005). Taken together these findings suggest that anxiety may interact with different types of awareness; at both global and local levels. The current healthy sample did not exhibit clinical levels of anxiety *or* depression; however, a more thorough investigation of emotional functioning and awareness is warranted to understand the direction of causality between emotional change and awareness.

A further caveat is the relatively small sample size for group correlations; nevertheless, the findings from this exploratory study generate interesting hypotheses that should be addressed in future studies of normal and abnormal patterns of self-awareness.

In conclusion, these results suggest that accurate metacognitive awareness in neurologically healthy participants may depend on efficient sustained attention functioning, supporting the role of frontal control systems in neuroanatomical models of self-awareness. Studies of awareness in clinical patient groups should pay careful attention to levels of metacognitive awareness among control participants, since such levels may also fluctuate considerably among young healthy adults. The following chapters will examine the role of frontal control systems for self-awareness further, by systematically exploring self-awareness impairments among unilateral frontal and non-frontal focal lesion patients.

Chapter 3 : The Neural Basis of Self-Awareness – Different Roles for Left and Right Prefrontal Cortices

Abstract

Self-awareness deficits after brain injury represent a significant clinical and theoretical challenge, and relatively little is known about the neuroanatomical correlates of this type of disorder. The aim of this study was to systematically compare the effects of specific focal cortical lesions on a number of self-awareness measures, with particular emphasis on assessing the role of left and right prefrontal cortices. Results showed that both left and right frontal lesion patients exhibited impaired metacognitive awareness, while right frontal lesion patients showed an additional significant deficit in monitoring errors as they occurred, and in their autonomic response to aware errors. Left frontal lesion patients, in contrast, showed initially poor anticipatory awareness, but appropriately adjusted their estimate downward following task completion, suggesting relatively intact error responsiveness. These findings suggest separate mechanisms for self-awareness disturbances following left and right prefrontal injury: In left frontal lesion patients, poor metacognitive and anticipatory awareness may be mediated by memory or other cognitive impairments. Right prefrontal cortex on the other hand is crucial for processing errors on a moment-to-moment basis, potentially by providing top-down control over autonomic arousal levels.

3.1 Introduction

As the review of the literature in Chapter 1 has demonstrated, there are a number of findings which point to the particular importance of the frontal lobes for intact self-awareness, and this is reflected in neuroanatomical models such as that of Stuss and colleagues (Stuss, 1991; Stuss & Benson, 1986; Wheeler et al., 1997). Additionally, the results from Chapter 2, where self-awareness was examined among non-neurological young adults, also implicated frontal lobe networks for self-awareness. Some neuroimaging results appear to support such a view, showing medial PFC activation associated with conscious self-reflection (e.g., Gusnard et al., 2001; Johnson et al., 2002). These studies, however, are correlational in nature, and cannot establish the necessity of individual brain regions for self-awareness.

In order to establish the relative contribution of individual brain regions to accurate self-awareness, the impact of specific, circumscribed neural dysfunction on measures of self-awareness must be examined. Numerous studies have shown that self-awareness can be impaired following wide-spread injury such as Traumatic Brain Injury (TBI) (e.g. Prigatano, 2005), degenerative disease such as Alzheimer's Disease (AD) and Frontotemporal Dementia (FTD) (Migliorelli et al, 1995; O'Keeffe, Murray et al, 2007), however, even moderately precise brain-behaviour relationships are difficult to establish in these patient groups.

In neurological studies, a significant problem is the use of one patient group to establish self-awareness deficits, thereby providing no way to directly compare the effects of damage to different brain regions to each other. For example, although it is widely acknowledged that anosognosia for hemiplegia is typically associated with right fronto-parietal dysfunction (see Orfei, Robinson, Prigatano et al., 2007; Pia et al., 2004, for recent reviews), a frequent criticism of right hemisphere models of self-awareness is that potential unawareness syndromes following left hemisphere lesions may frequently be missed because of language impairments in such patients, and that language and inner speech are themselves important for accurate self-awareness (Morin, 2002; Morin & Michaud, 2007). Nonetheless, there is evidence to suggest that right hemisphere structures, and specifically right prefrontal cortex, may play a particularly important role, as Chapter 1 has shown.

In summary, the neuroanatomical basis of self-awareness requires better definition (e.g. Orfei, Robinson, Bria et al., 2007), and no single study has comprehensively and systematically examined self-awareness deficits in groups of patients with focal lesions. Using the theoretical distinctions between metacognitive, online emergent and online anticipatory awareness (Crosson et al, 1989; Toglia & Kirk, 2000) has previously been helpful in highlighting the neuropsychological characteristics of TBI patients with high or low self-awareness (O'Keeffe, Dockree, et al., 2007), and also those with degenerative illness affecting frontal systems functioning (O'Keeffe, Murray et al., 2007). More specific examination of the contribution of unilateral frontal and non-frontal lesions to problems in self-awareness is required, with one emerging hypothesis from the literature being that right prefrontal cortex lesions may

have a particularly prominent effect on self-awareness. Previous studies have shown that impaired self-awareness may be mediated by poor processing of errors associated with lowered autonomic response to errors as shown by skin conductance responses (SCR) (O'Keeffe et al., 2004), which Damasio (1994) has termed 'somatic markers'. The current study aims to extend those previous findings to patients with discrete focal lesions, by examining metacognitive and online (anticipatory and emergent) self-awareness in patients with documented left or right prefrontal, and left or right non-frontal neural injury.

3.2 Method

3.2.1 Participants

Patients for this study were recruited on a voluntary basis through the Department of Psychology in Beaumont Hospital, Dublin, using the following inclusion criteria: Patients must be between the ages of 18 and 70 years, and have received a diagnosis of a discrete focal brain lesion in any of the four cortical regions specified – right or left frontal, right or left non-frontal cortex, with the additional requirement that lesions did not include the motor cortex. Patients were also excluded from the study if any of the following applied: a history of alcohol/substance abuse, diagnosis of a major psychological/psychiatric disorder, or any additional neurological disorder. This led to a sample of 13 right frontal (RF), 12 left frontal (LF), as well as 14 right non-frontal (RNF) and 18 left non-frontal (LNF) focal lesion patients. Table 3.1 displays the clinical details for each patient, including diagnosis, Time Since Lesion (TSL) and the type of clinical brain scan available. MRI scans were available for 30 patients, while CT images were provided for 18 patients. Representative slices of patients' CT or MRI scans are shown in Figure 3.1a-3.1d. Since patients' scans were clinical in nature and thus varied considerably in orientation and other parameters, lesions are shown on an individual basis, rather than reconstructed lesion maps.

Patient groups did not differ on mean Time Since Lesion (TSL) [$F(3, 53) = 1.358$, $p > 0.05$].

A sample of 20 healthy volunteer participants served as a control group. Exclusion criteria were the same as for patients, with the additional requirement that control participants must never have suffered a head injury leading to a loss of consciousness or memory.

Ethical approval for the study was obtained from the research ethics committees of Beaumont Hospital and Trinity College Dublin. Informed consent was obtained from all participants according to the Declaration of Helsinki. All participants received reimbursement for travel expenses.

Table 3.1. Clinical Data for Focal Lesion Patients.

Patient ID	Diagnosis	TSL (Months)	Neuro-Imaging
	LF Group		
008 OC	Grade III Glioma	65	CT
016 MF	Anaplastic Glioma	36	MRI
047 PC	Low Grade Glioma	29	MRI
115 BD	Contusion (HI)	91	CT
239 BM	Lacunar Infarct	86	CT
291 JOR	High Grade Glioma (Resected)	144	MRI
348 RS	Grade II Glioma	47	MRI
352 OB	Grade II Glioma	31	MRI
355 DJ	Grade II Glioma	15	MRI
356 JD	Grade III Glioma	15	MRI
360 JOR	Grade I Meningioma	17	MRI
363 BMG	ACA Aneurysm (Coiled)	23	MRI
	RF Group		
021 PH	Medial FL Aneurysm (Clipped)	30	CT
090 BBD	High Grade Glioma	72	CT
164 MH	AVM (Embolization)	79	MRI
169 JW	Subdural Abscess	160	N.A.
216 AMC	AVM with Associated Haemorrhage	125	N.A.
335 JB	Grade II Glioma	24	MRI
346 PF	Grade III Glioma (Debulked)	33	N.A.
350CH	Meningioma with Associated Haemorrhage	26	MRI
353 SK	Grade IV Glioma	11	MRI
359 MS	Carcinoma (Debulked)	10	N.A.
361 KG	Grade III Glioma (Debulked)	12	MRI
362 AB	Grade IV Glioma (Debulked)	7	MRI
364 AP	Meningioma (Debulked)	6	N.A.
	LNF Group		
002 CFB	Parieto-Occipital AVM	94	MRI
049 GC	Temporal Lobe Meningioma	43	MRI
055 CK	Temporal Lobe Haemorrhage (HI)	29	N.A.
152 BG	Inferior Occipital Lobe Atrophy	153	N.A.
161 CG	PCA Aneurysm	99	CT
166 JC	Temporo-Occipital Subdural Haematoma	74	CT
170 PH	Temporo-Parietal AVM	122	N.A.
259 SM	Parietal Cavernous Angioma & Intracranial Haematoma	154	CT
266 VM	MCA Aneurysm (Clipped)	147	CT
328 SW	Temporo-Parietal Low Grade Glioma	148	MRI
334 MU	Focal Cortical Atrophy in Posterior Parietal/Occipital Lobe	144	MRI
336 PC	Occipital Haemorrhage due to Suspected AVM	17	CT
338 GC	Mesial Temporal Low Grade Glioma	34	MRI
339 MF	Mesial Temporal Sclerosis (Hippocampectomy)	55	MRI
340 CE	Temporal Pole Cavernous Angioma	12	N.A.
344 SR	Parietal Low Grade Glioma	29	MRI
345 AP	Parieto-Occipital AVM with Associated Haemorrhage	11	MRI
347 AA	PCA aneurysm (Coiled)	20	CT

	RNF Group		
046 AB	MCA Territory Non-Haemorrhagic Infarction	20	CT
066 GON	Inferior Temporal Extradural Haematoma	20	CT
086 CB	Occipito-Parietal Haemorrhage & Haematoma	113	MRI
088 WB	Parietal Skull Fracture (HI)	134	CT
162 PH	PCA aneurysm (Clipped)	118	CT
261 MM	Hippocampal sclerosis (Hippocampectomy)	102	N.A.
337 CC	Temporal Lobe AVM (Excised)	10	CT
341 GC	Cavernous Haemangioma (Resected)	66	CT
342 MK	Hippocampal sclerosis (Anterior Hippocampectomy)	31	MRI
343 GF	Hippocampal Sclerosis (Anterior Hippocampectomy)	28	MRI
349 MON	Mesial Temporal Sclerosis	36	MRI
351 EM	Mesial Temporal Sclerosis (Hippocampectomy)	30	MRI
357 EQ	Mesial Temporal Sclerosis (Amygdalo-Hippocampectomy)	16	MRI
358 EB	Temporal Grade II Meningioma	13	MRI

Abbreviations: ACA = Anterior Cerebral Artery; AVM = Anteriovenous malformation; CT = Computerized Tomography; HI = Head Injury; LF = Left Frontal; LNF = Left Non-Frontal; MCA = Middle Cerebral Artery; MRI = Magnetic Resonance Imaging (structural); N.A. = Not Available; PCA = Posterior Communicating Artery; RF = Right Frontal; RNF = Right Non-Frontal; TSL = Time Since Lesion.

Note: Clinical brain scans were unavailable for some patients as indicated, however, consultants' lesion descriptions are provided for all patients.

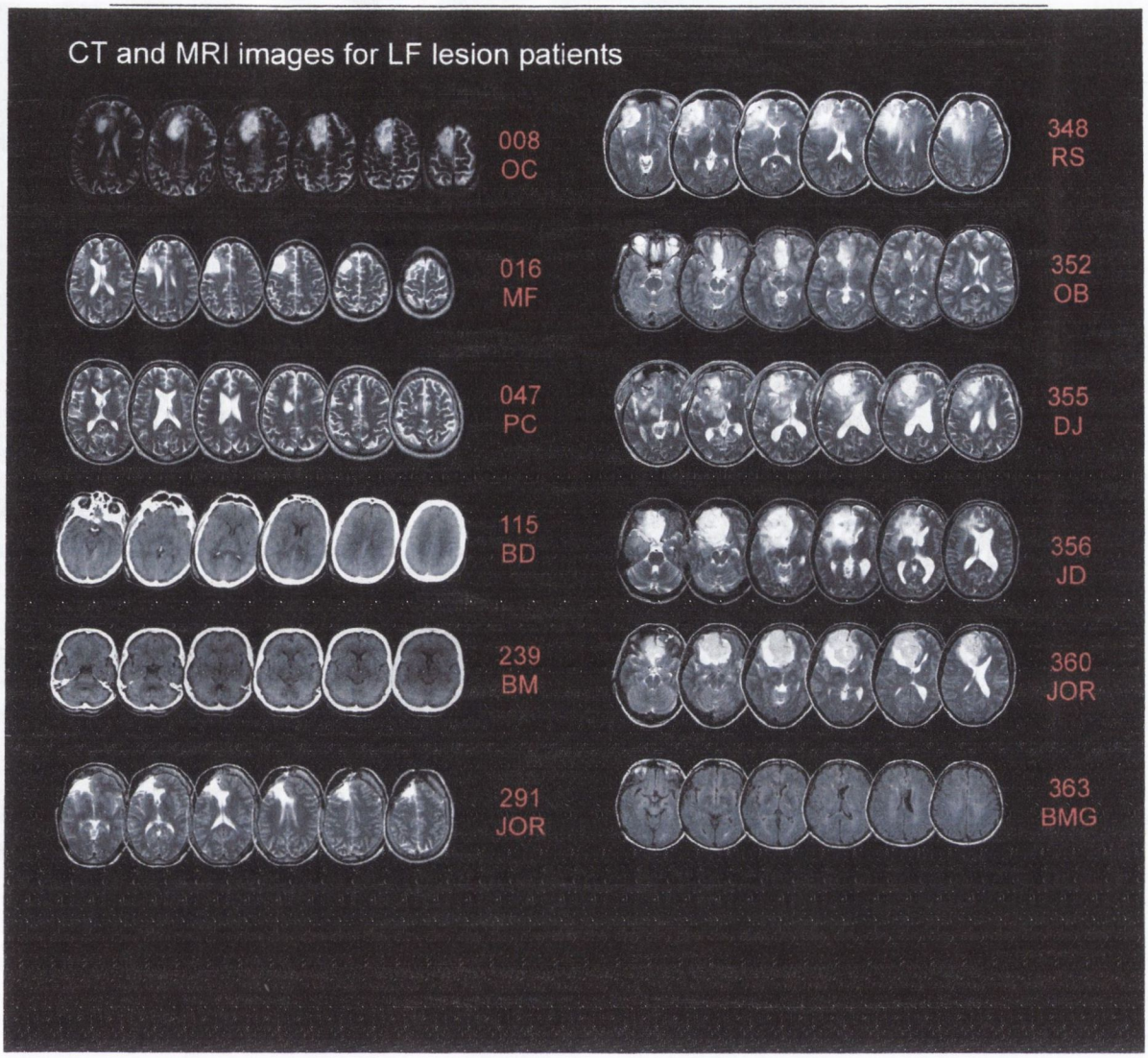


Figure. 3.1a. Clinical CT and MRI images for LF lesion patients.

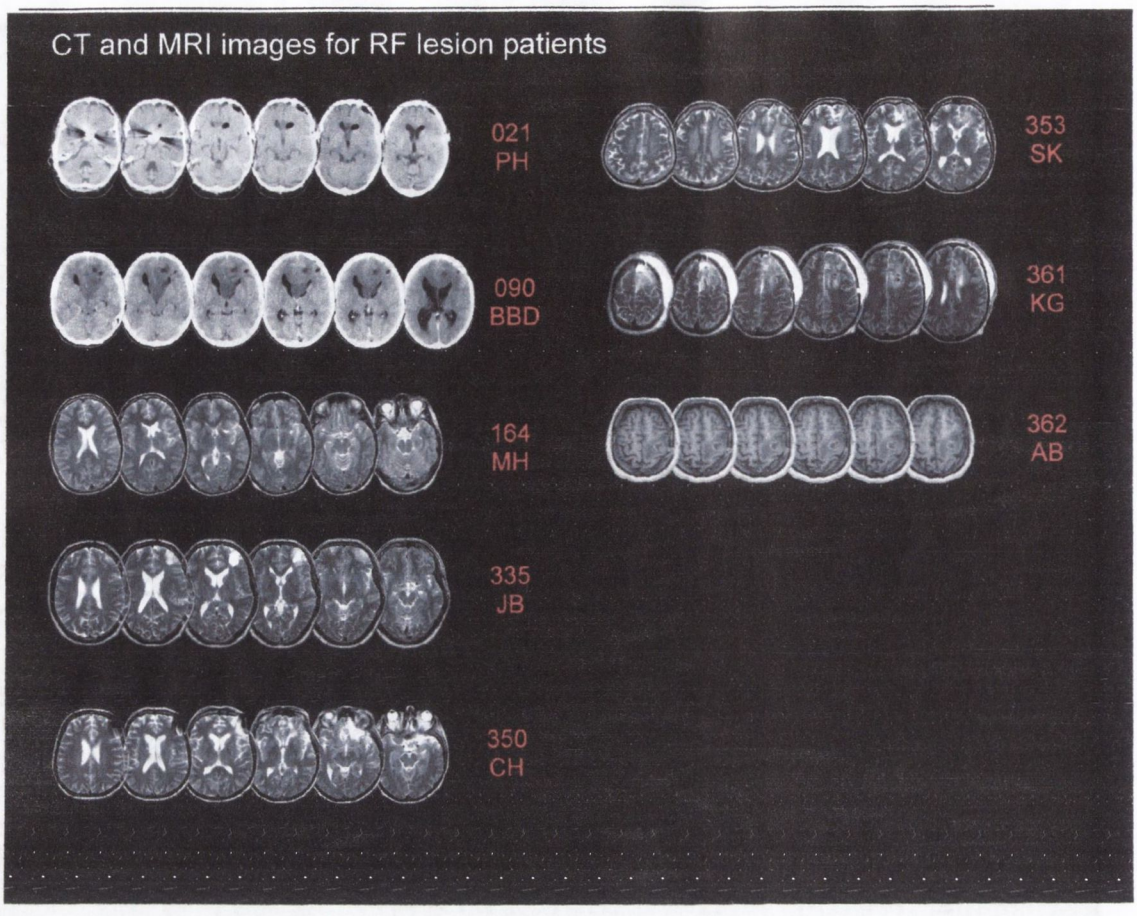


Figure 3.1b. Clinical CT and MRI images for RF lesion patients.

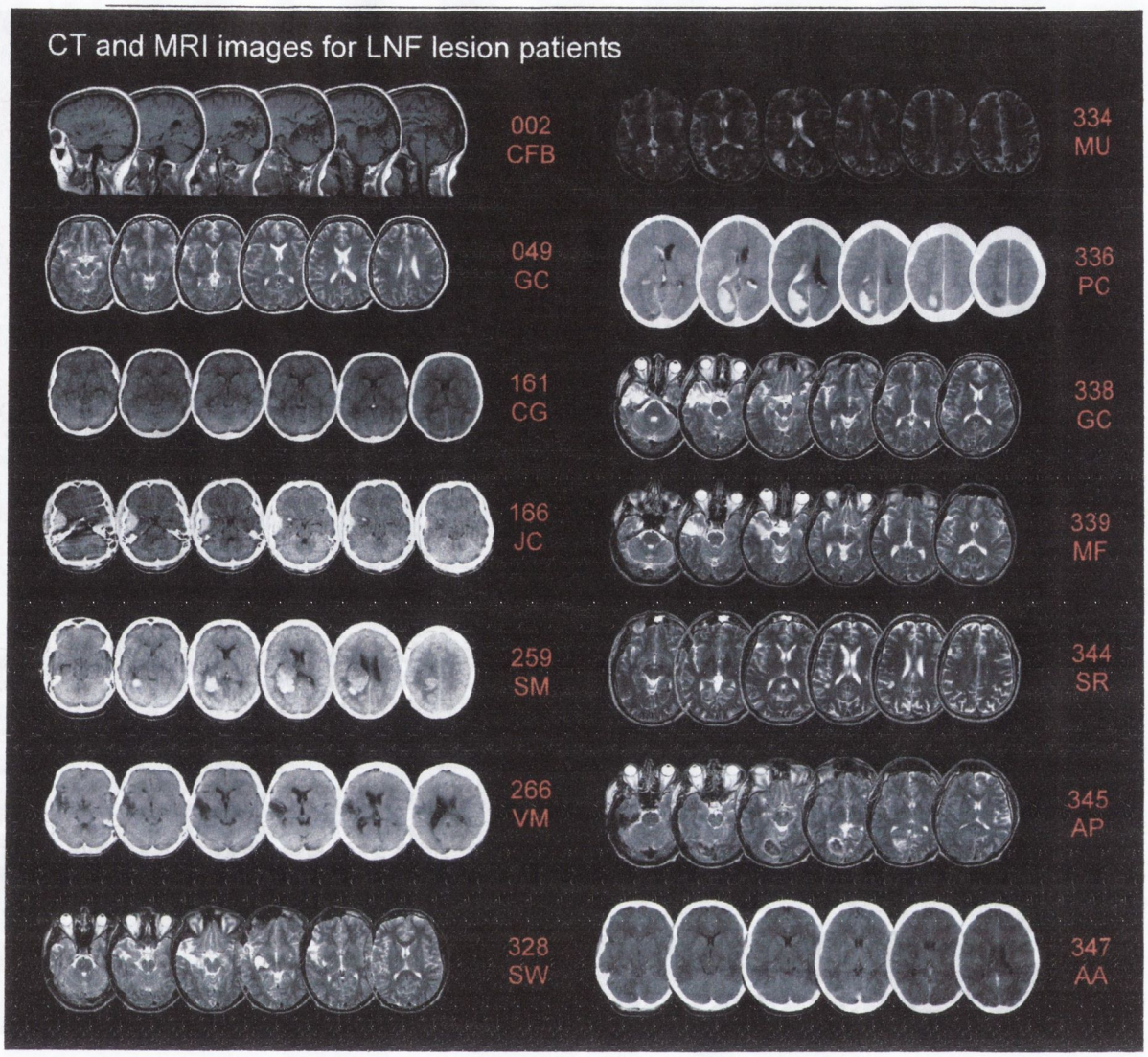


Figure 3.1c. Clinical CT and MRI images for LNF lesion patients.

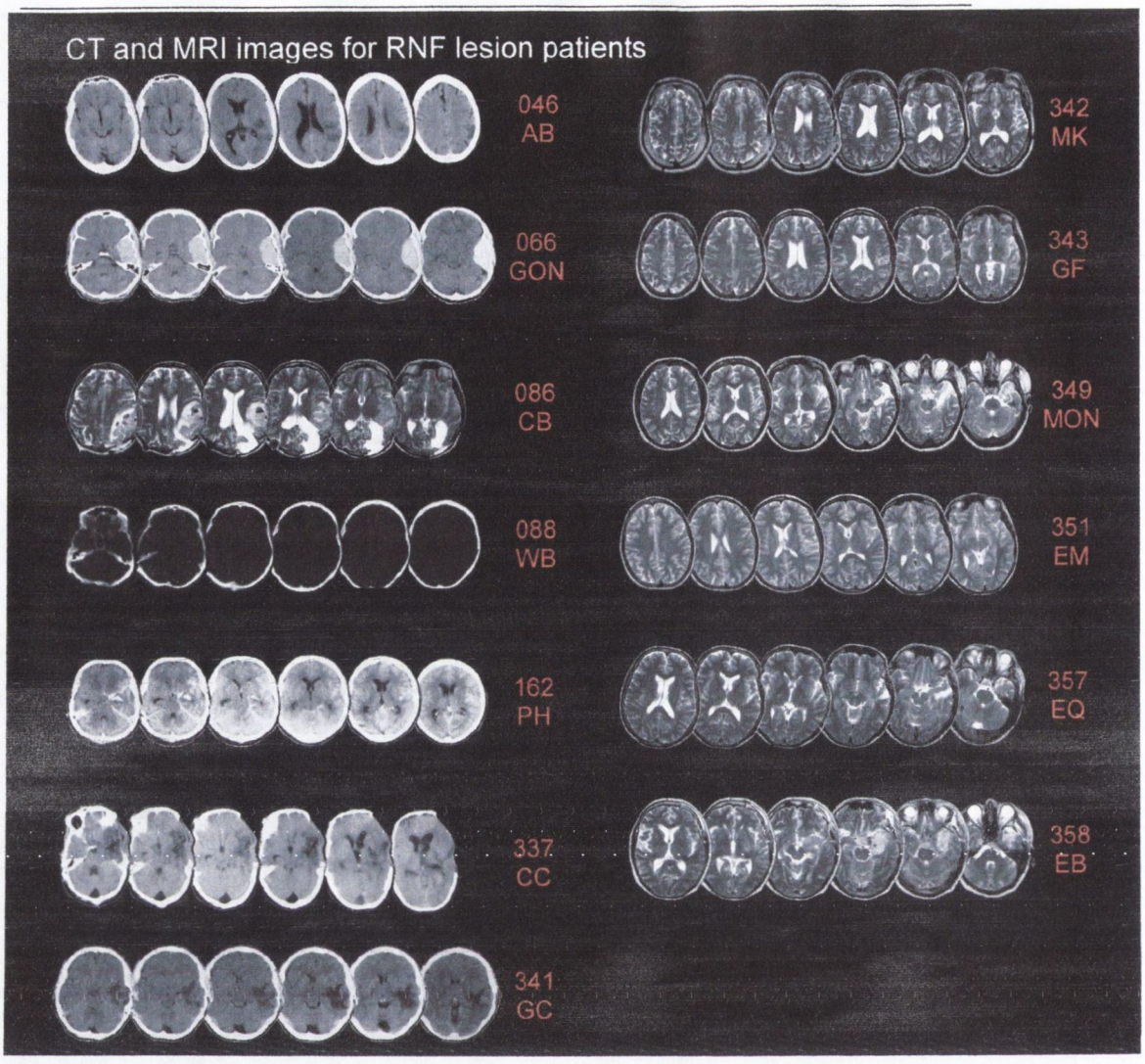


Figure 3.1d. Clinical CT and MRI images for RNF lesion patients.

3.2.2 Materials and Procedure

All participants completed a testing session of approximately 2.5 hours, which included all of the following measures:

3.2.2.1 Screening Measures

Premorbid IQ. Revised National Adult Reading Test for premorbid IQ estimate (NART-R; Nelson, 1982; Nelson & Willison, 1991).

General Orientation. Orientation and Information subtest of the Wechsler Memory Scale (WMS III; Wechsler et al., 1998).

Aphasia. Frenchay Aphasia Screening Test (FAST; Enderby, Wood, Wade, & Hewer, 1987).

Visuospatial Impairment. Shape Detection subtest of the Visual Object and Space Perception Battery (VOSP; Warrington & James, 1991), where a score below 15 indicates visuospatial deficit.

Unilateral Neglect. Bells Test (Gauthier, Dehaut, & Joanette, 1989), where a cut-off point of more than three missed bells on the left side of the page was used to indicate neglect.

Emotional Functioning. Hospital Anxiety and Depression Scale (HADS; Zigmond & Snaith, 1983) for symptoms of anxiety and depression.

3.2.2.2 Neuropsychological Tasks

Memory. Subtests from the Wechsler Memory Scale (Wechsler et al, 1998): Logical Memory – Immediate and Delayed, Digit Span and Spatial Span, Faces – Immediate and Delayed.

Attention - Visuomotor Attention. Trail Making Test (TMT; Partington & Leiter, 1949) – Time B minus Time A.

Attention – Sustained Attention. Participants were required to perform 3 blocks of the fixed-sequence version of the Sustained Attention to Response Task (SART; Robertson, Manly, Andrade, Baddeley, & Yiend, 1997; Manly et al., 2003). Figure 3.2 shows an example of the stimuli used, along with stimulus durations and ISIs. Participants were instructed to press the left mouse button for all numbers presented in fixed ascending sequence, and withhold responses for the number '3'. The SART score reflects the percentage of commission errors across all blocks (commission errors / number of no-go targets X 100).

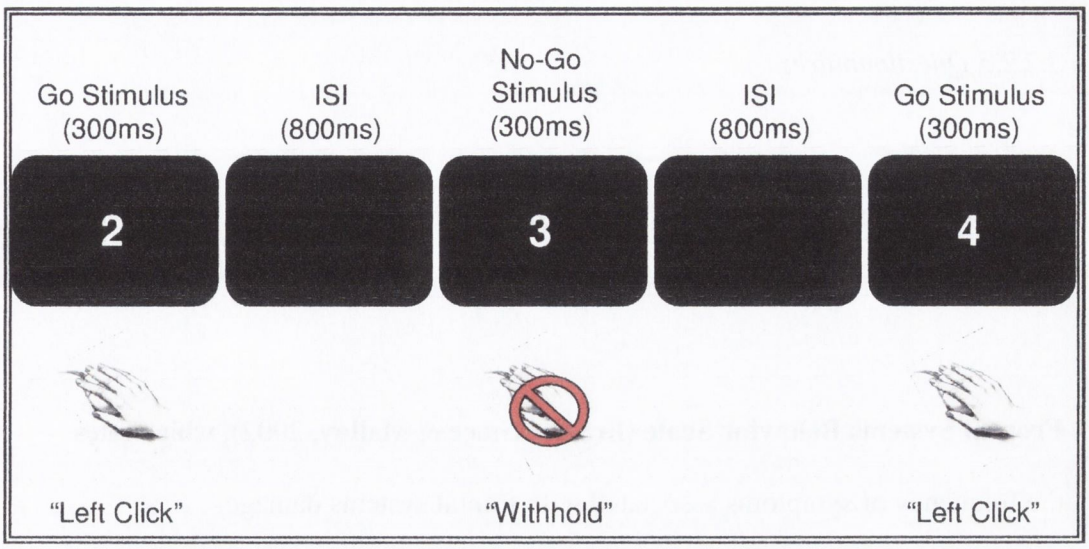


Figure 3.2 SART Task Schematic. Shows an example of the fixed sequence of SART digits. Participants respond with a left button click for every number and withhold for number 3.

Executive Functions. Self-Ordered Pointing Task (SOPT; Petrides & Milner, 1982). Participants are presented with pages of identical abstract designs, arranged in a different order on each page. The task is to point to a different design on each page, without pointing to any one design more than once. The total number of errors served as the score.

Verbal fluency (letters F, A and S) and category fluency (animals) (Spreen & Strauss, 1998). The total number of items generated during 60 seconds served as the score.

3.2.2.3 Questionnaires

Cognitive Failures Questionnaire (CFQ; Broadbent et al., 1982), which rates the frequency of everyday cognitive failures and absentmindedness.

Frontal Systems Behavior Scale (FrSBe; Grace & Malloy, 2002), which rates the frequency of symptoms associated with frontal systems damage.

Patient Competency Rating Scale (PCRS; Prigatano & Fordyce, 1986), which rates participants' competencies on activities of daily living, interpersonal, cognitive and emotional competencies.

All questionnaires were administered both to participants themselves and their significant others[1].

3.2.2.4 Awareness Measures

3.2.2.4.1 Perception of Behavioural Change Since Injury

Change in behaviour since injury was assessed by subtracting FrSBe scores 'before injury/illness' from those 'at present'. This was computed both for participants and their significant others.

[1] Note: Higher scores indicate higher *symptoms* on the CFQ and FrSBe, while higher scores indicate higher *competencies* on the PCRS.

3.2.2.4.2 Metacognitive Awareness

Metacognitive awareness scores were derived from discrepancies between self- and other ratings on the CFQ, FrSBe and PCRS ('self' minus 'other' for CFQ and FrSBe; 'other' minus 'self' for PCRS), so that negative discrepancy scores indicate an under-estimation of difficulties. A compound z-score served as the metacognitive awareness scores.

3.2.2.4.3 Online Awareness

Online Emergent Awareness on SART – participants were required to indicate awareness of commission errors on the SART verbally ('Hit').

Online Anticipatory and Emergent Awareness on Cognitive Tasks – participants were asked to estimate how well they would perform on four cognitive tasks (Digit Span, Spatial Span, Verbal Fluency and Category Fluency). Estimates were obtained *before* and *after* participants completed the task. Mean accuracy was then calculated for estimates *before task completion* (indexing *anticipatory awareness*) and *after task completion* (indexing emergent awareness). Mean accuracy was calculated using the formula "Prediction / Performance X 100". Values above 100 indicate that participants *over*-estimate how well they could perform, while values below 100 indicate *under*-estimation of performance.

3.2.2.5 Skin Conductance Response (SCR) during SART

SCR was measured during SART performance, using a Biopac Systems Inc. MP30 unit, electrodes and software (www.biopac.com). Two Ag/AgCl electrodes, mounted in individual housings and shielded to minimize noise interference, were filled with SIGNA® gel and attached to the distal phalanges of the index and middle fingers of participants' non-dominant hand. SCR signals were converted to digital signals via the MP30 unit and processed with BIOPAC Student Lab PRO for offline analysis. For SCR amplitude measurements, a latency window of 1-5 seconds following presentation of no-go targets (digit '3') was specified. SCR amplitudes (μS) reflect conductance at the peak minus conductance prior to the response, as defined by Stern, Ray, & Quigley (2001). The criterion for the smallest scorable SCR was set at 0.02 μS. SCR amplitudes were averaged separately for correct withholds and aware errors.

3.3 Results

3.3.1 Demographic and Screening Results

Demographic, screening and neuropsychological data for each patient group and controls are presented in Table 3.2. Groups did not differ on key demographic variables, including gender [$\chi^2 = 0.183$, df = 4, $p > 0.05$], age [$F(4, 72) = 0.40$; $p > 0.05$], or years of education [$F(4,72) = 2.379$, $p > 0.05$] and WMS Orientation [$F(4,72) = 2.344$; $p > 0.05$]. One group difference emerged for premorbid IQ [$F(4,72) = 6.165$, $p < 0.01$], with Bonferroni comparisons showing that RNF lesion patients had lower premorbid IQ scores than both controls and RF lesion patients (both $p < 0.01$). As a result, all subsequent group comparisons were conducted while covarying for premorbid IQ scores.

All participants performed sufficiently well on the screening measures for visuospatial function, unilateral neglect and aphasia to rule out impairment (i.e. no participant scored above/below the cut-off scores specified for each test). No group difference existed for anxiety or depression scores (both $p > 0.05$).

3.3.2 Neuropsychological Performance

Separate univariate ANOVAs, followed by Bonferroni comparisons, showed that group differences existed on a number of neuropsychological and questionnaire measures. This is detailed in Table 3.2, showing mean raw scores (unless otherwise indicated) for all groups.

On memory performance, LF lesion patients differed significantly from controls on digit span [$F(4, 71) = 2.766$; $p < 0.05$], while LNF patients scored significantly lower than controls on WMS Immediate Face Recognition [$F(4, 71) = 3.103$; $p < 0.05$]. On delayed WMS face recognition, RF patients showed poorer performance than controls [$F(4, 71) = 3.777$; $p < 0.05$].

An effect of group also existed on TMT scores (TMT B minus TMT A) [$F(4, 71) = 5.447$; $p < 0.01$], and Bonferroni comparisons showed that LF patients differed significantly from controls and from RNF patients (both $p < 0.05$), by showing larger discrepancy between TMT Time B and TMT Time A. On sustained attention scores, LF lesion patients performed significantly poorer than controls [$F(4, 71) = 2.532$, $p < 0.05$].

On measures of executive function, a main effect of group for SOPT errors and category fluency approached significance (SOPT errors: $p = 0.089$; category fluency: $p = 0.058$). Groups did, however, differ significantly on verbal fluency [$F(4, 71) = 4.905$, $p < 0.01$], with Bonferroni comparisons highlighting that LF and LNF patients showed poorer verbal fluency than controls (all $p < 0.05$).

3.3.3 'Other'-Rated Questionnaires

On questionnaire ratings provided by significant others, groups differed on everyday cognitive failures, as indexed by on the CFQ (Other) scores [$F(4, 71) = 2.507$, $p = 0.05$]. Bonferroni comparisons revealed that the difference between LF patients and controls fell just short of statistical significance ($p = 0.056$). Furthermore, LNF lesion patients showed significantly lower everyday competency than controls [$F(4, 71) = 2.648$, $p < 0.05$], as indexed by PCRS (Other) scores. For FrSBe Total (Other) scores, no main effect of group emerged ($p > 0.05$). The results of these group comparisons are also displayed in Table 3.2 below.

Table 3.2 Demographic and Neuropsychological Data for all Groups.

	LF	RF	LNF	RNF	C	P-Value
Demographics & Screening						
N (Gender: m, f)	12 (6, 6)	13 (6, 7)	18 (8, 10)	14 (7, 7)	20 (10, 10)	0.996
Age (SD)	46.6 (10.1)	43.9 (13.4)	43.9 (11.8)	40.6 (13.7)	42.6 (12.7)	0.808
Education (Years) (SD)	13.5 (4.1)	15.0 (2.6)	16.1 (3.6)	15.0 (2.6)	16.3 (1.7)	0.060
NART-IQ (SD)	111.6 (8.5)	118.3 (5.7)[a]	113.1 (9.0)	105.7 (13.9)[ab]	119.4 (4.2)[b]	**0.000**
WMS Orientation (SD)	12.4 (0.8)	13.0 (0.6)	13.1 (0.8)	12.9 (0.8)	13.2 (0.6)	0.063
Frenchay Aphasia Screening	N. I.	N. I.	N. I.	N. I.	N. I.	---
VOSP Shape Detection	N. I.	N. I.	N. I.	N. I.	N. I.	---
Bells Test for Neglect	N. I.	N. I.	N. I.	N. I.	N. I.	---
HADS Anxiety (SD)	6.5 (3.7)	6.2 (3.4)	6.9 (4.4)	6.9 (3.4)	5.5 (2.2)	0.935
HADS Depression (SD)	3.2 (2.7)	3.0 (3.2)	4.8 (4.1)	3.9 (3.5)	2.7 (2.0)	0.478
Memory						
Logical Memory -Immediate (SD)	32.1 (13.0)	40.6 (9.1)	37.7 (13.6)	38.4 (9.8)	45.3 (9.3)	0.119
Logical Memory -Delayed (SD)	18.8 (11.1)	23.4 (7.2)	24.2 (11.4)	22.1 (9.7)	29.4 (7.3)	0.142
Digit Span (SD)	14.0 (4.7)[c]	18.2 (3.5)	17.8 (4.8)	16.3 (4.4)	20.5 (4.1)[c]	**0.034**
Spatial Span (SD)	12.0 (3.5)	15.5 (2.2)	15.1 (4.1)	13.0 (4.0)	15.7 (3.6)	0.190
Faces -Immediate (SD)	35.5 (5.7)	36.8 (3.8)	35.6 (5.1)[d]	34.5 (5.9)	41.0 (2.9)[d]	**0.021**
Faces -Delayed (SD)	36.3 (5.4)	36.2 (5.1)[e]	36.5 (5.5)	34.6 (5.4)	41.8 (2.8)[e]	**0.008**
Attention						
Visuomotor - TMT (B-A) (SD)	128.0 (81.5)[c]	72.8 (26.3)	80.5 (49.6)	77.3 (41.5)[f]	41.7 (28.0)[cf]	**0.001**
Sustained - SART Errors (%) (SD)	12.3 (7.2)[c]	9.2 (6.6)	9.7 (5.9)	9.9 (8.9)	4.5 (3.0)[c]	**0.048**
Executive Function						
SOPT Errors (SD)	7.9 (2.4)	6.4 (2.7)	8.8 (1.9)	7.8 (2.4)	6.6 (2.7)	0.089
Verbal Fluency (SD)	28.9 (7.2)[c]	41.5 (12.2)	33.0 (12.1)	33.1 (13.9)	49.4 (12.6)[c]	**0.002**
Category Fluency (Animals) (SD)	17.5 (8.7)	19.6 (6.7)	21.1 (6.1)	20.6 (6.5)	24.8 (4.2)	0.058
'Other' Questionnaire Ratings						
CFQ (Other) (SD)	15.4 (6.6)[c]	10.2 (7.4)	13.5 (3.9)	13.0 (7.3)	8.7 (4.7)[c]	**0.005**
FrSBe (Other) (SD)	91.1 (25.5)	93.6 (32.9)	96.7 (11.4)	92.6 (31.6)	75.1 (13.2)	0.124
PCRS (Other) (SD)	120.2 (24.5)	127.6 (23.0)	120.2 (8.8)[d]	120.3 (20.2)	137.6 (7.8)[d]	**0.040**

Abbreviations: C = Control Group; CFQ = Cognitive Failures Questionnaire; FrSBe = Frontal Systems Behavior Scale; HADS = Hospital Anxiety And Depression Scale; LF = Left Frontal Lesion Group; LNF = Left Non-Frontal Lesion Group; NART = National Adult Reading Test; N. I. = No Impairment detected; PCRS = Patient Competency Rating Scale; RF = Right Frontal Lesion Group; RNF = Right Non-Frontal Lesion Group; SART = Sustained Attention to Response Task; SOPT = Self-Ordered Pointing Test; TMT = Trail Making Test; VOSP = Visual Object and Space Perception Battery; WMS = Wechsler Memory Scale (III).

Bonferroni comparisons: [a] RF vs RNF ($p < 0.05$); [b] RNF vs C ($p < 0.05$); [c] LF vs C ($p < 0.05$); [d] LNF vs C ($p < 0.05$); [e] RF vs C ($p < 0.05$); [f] LF vs RNF ($p < 0.05$).

3.3.4 Perceptions of Behavioural Change since Injury

Perceived change in behaviour was calculated both from the 'self' and 'other' version of the FrSBe and compared for each patient group, in order to highlight whether patients' perception of behavioural change differed from that of their significant others[2]. A repeated measures ANOVA with Behavioural Change Rating (2 levels: 'self' or 'other' rating) as within-subjects factor, and Group (4 levels: LF, RF, LNF and RNF) as between-subjects factor, was performed. The results showed that no significant main effect existed for group [$F(3,51) = 0.663$, $p > 0.05$] or Behavioural Change Rating [$F(1,51) = 0.115$, $p > 0.05$]. However, a significant interaction between the two factors existed [$F(3, 51) = 2.937$, $p < 0.05$]. Separate follow-up paired t-tests showed that LF lesion patients rated themselves significantly lower on behavioural change since injury, compared to ratings obtained from their significant others ($t = -3.564$, $df = 11$, $p < 0.01$). For RF lesion patients, the same pattern emerged, with a trend towards statistical significance ($t = -2.1$, $df = 11$, $p = 0.06$). Both non-frontal lesion groups showed no significant difference in perception of behavioural change between 'self' and 'other' ratings (both $p > 0.05$). 'Self' and 'other' ratings of behavioural change for all patient groups are displayed in Figure 3.3 below.

[2] For one RF patient, FrSBe (Other) scores from the 'before injury/illness' subscale were not available, therefore N = 56 for this analysis.

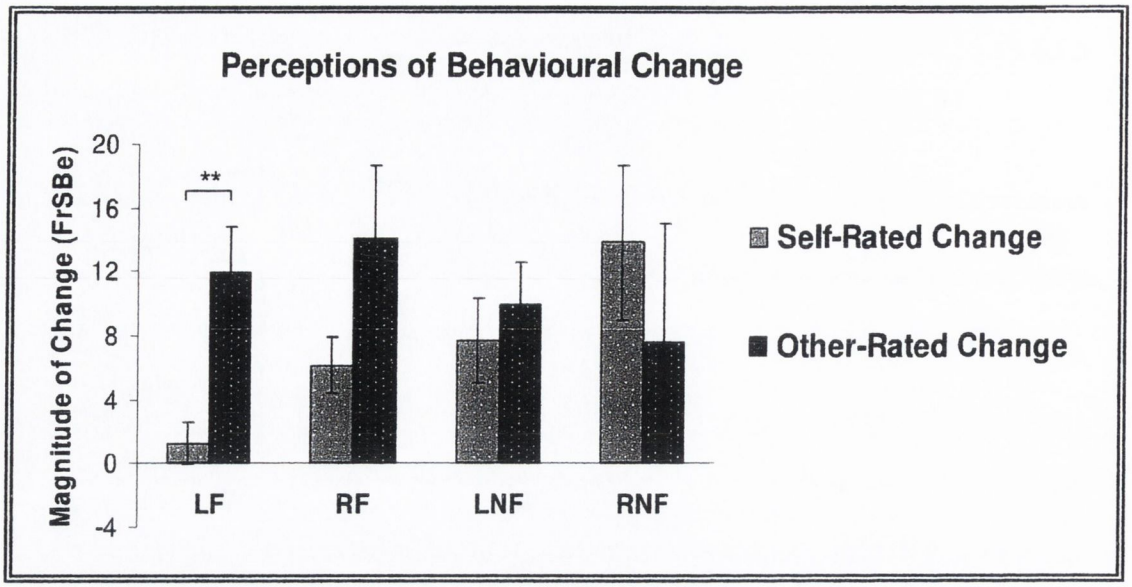


Figure 3.3. 'Self' and 'Other' – Ratings of Behavioural Change for Each Patient Group. Ratings of behavioural change made by LF lesion patients were significantly lower than those obtained from their significant others, suggesting that they did not perceive their increase in behavioural symptoms. The same pattern existed for the RF group, where the difference between 'self'- and 'other'-rated change showed a trend towards significance ($p = 0.060$). ** $p < 0.01$. Error bars represent the standard error of the mean.

3.3.5 Metacognitive Awareness

Metacognitive awareness scores were derived from the discrepancies between 'self' and 'other' scales on three questionnaires, the CFQ, PCRS and FrSBe. Discrepancies were converted into individual z-scores and subsequently combined into a compound z-score for metacognitive awareness. A univariate ANOVA showed a main effect of group [$F (4, 71) = 4.590$, $p < 0.01$]. Bonferroni comparisons showed that both LF and RF lesion patients had significantly lower metacognitive awareness scores than controls (both: $p < 0.01$; 0.05), suggesting that both frontal lesion patients under-estimated their difficulties. In contrast, both non-frontal patient groups, as well as controls, scored above zero, suggesting that they over-estimated their difficulties. Figure 3.4 displays mean z-scores and group differences for metacognitive awareness.

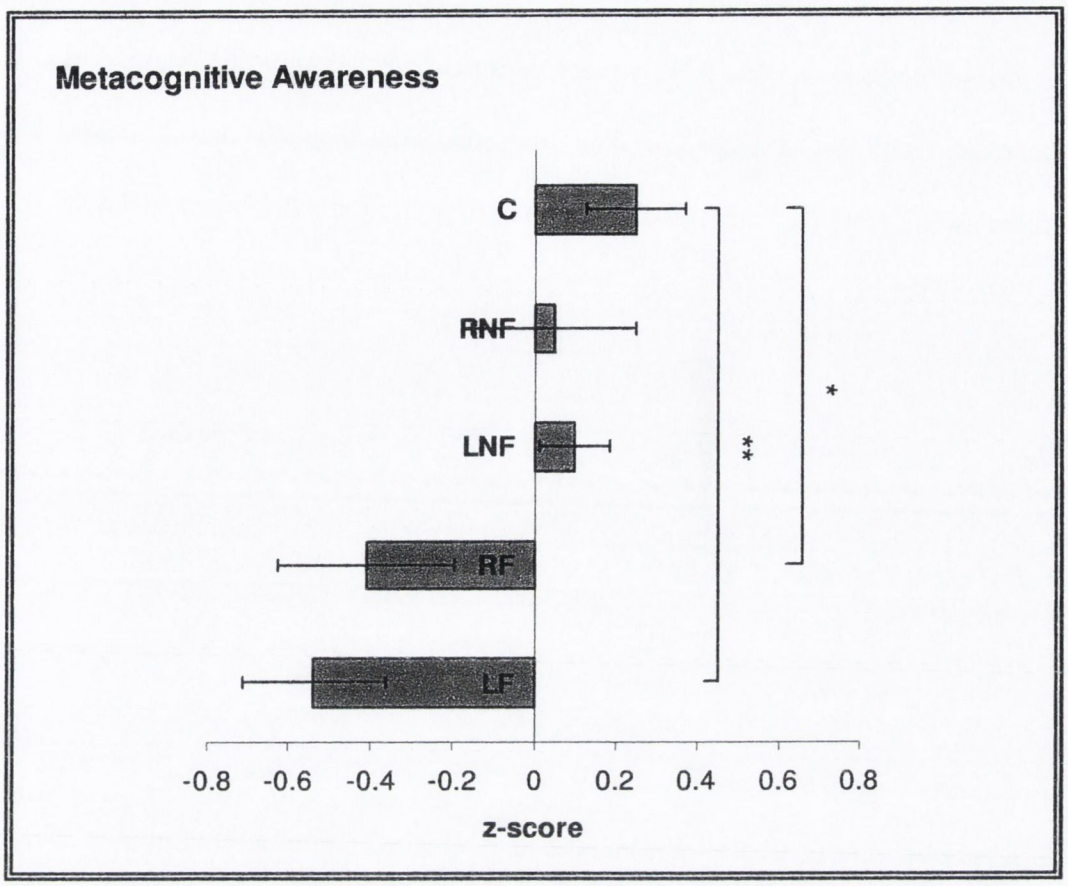


Figure 3.4 Metacognitive Awareness Scores for all Groups. Both RF and LF patients show significantly lower metacognitive awareness scores than controls, suggesting that these patients under-estimated their cognitive difficulties, while controls, by contrast, tended to over-estimate their difficulties.
* $p < 0.05$. ** $p < 0.01$. Error bars represent the standard error of the mean.

3.3.6 Online Awareness - Emergent

3.3.6.1 Error Awareness during SART

SART error awareness was defined as the percentage of all commission errors indicated as aware (Aware Errors / Total Errors X 100) during the SART. One

control participant and one RNF patient who made no commission errors was excluded from the analysis, leaving only participants with two or more commission errors. Mean number of errors committed are displayed in Table 3.3 below[3].

Table 3.3. Mean Number and Range of Commission Errors during SART for each Group.

	LF	RF	LNF	RNF	C
SART Commission Errors (Range)	14.63 (6-27)	10.00 (3-28)	9.00 (2-19)	8.91 (2-22)	5.22 (2-19)

A univariate ANOVA showed a main effect of group for awareness [$F(4, 69) = 3.311$, $p < 0.05$]. Bonferroni comparisons indicated significantly diminished error awareness among right frontal lesion patients, when compared to controls ($p < 0.01$). Figure 3.5 displays mean error awareness (%) as a function of group.

[3] Note: Two LF patients were not included in this descriptive analysis, since they only completed two blocks of SART. Their awareness scores, however, were included in all analyses, since they committed a total of 10 and 6 errors, respectively, i.e. > 2.

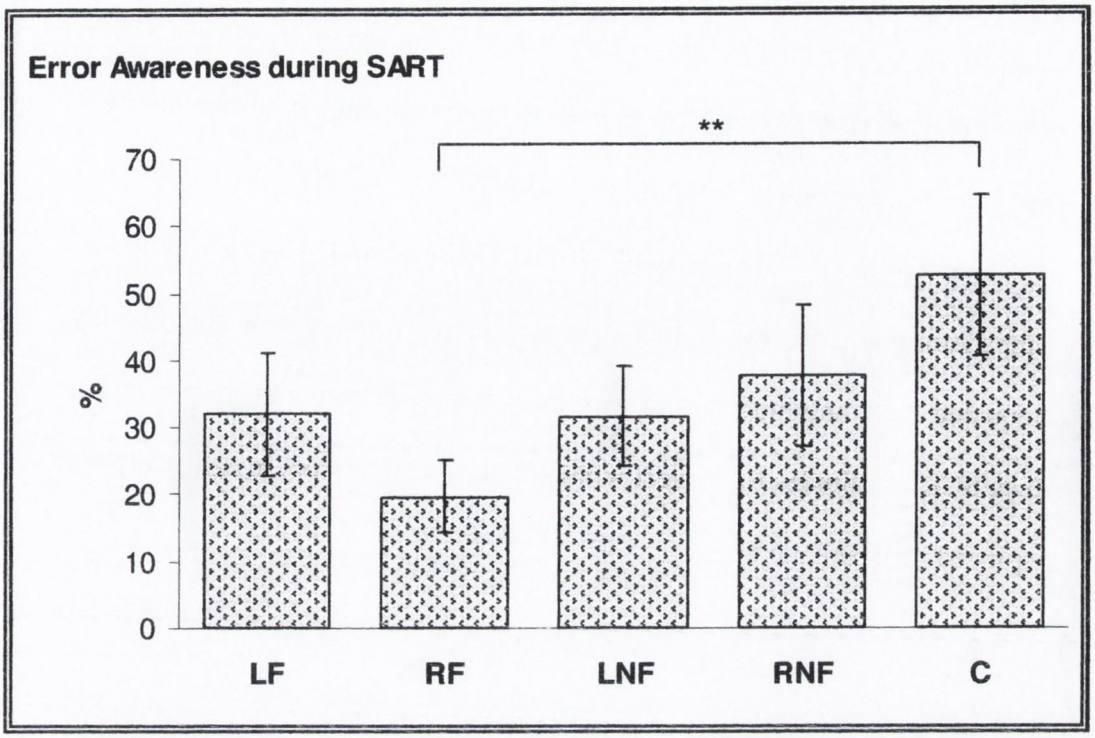


Figure 3.5. Mean Error Awareness during SART for Each Group. RF lesion patients showed significantly lower error awareness than control participants.
Note: Error bars denote the standard error of the mean. ** $p < 0.01$.

3.3.6.2 Skin Conductance Response to Errors

For SCR amplitude, groups were compared on correct withholds and errors reported as aware. Therefore, only participants who made more than one *aware* error are included in this analysis, leading to a reduced sample of 9 LF, 10 RF, 16 LNF, 11 RNF lesion patients, and 17 controls. A mixed ANOVA with Group as between-subjects factor (5 levels: LF, RF, LNF, RNF and Controls) and Condition as within-subjects factor (2 levels: Correct Withhold and Aware Error) was performed. The ANOVA showed a main effect of Group [$F(4,58) = 3.746$, $p < 0.05$), no main effect of Condition [$F(1,58) = 1.455$, $p > 0.05$], and

a significant Group by Condition interaction [F (4, 58) = 4.147, $p < 0.01$]. Follow-up univariate ANOVAs showed that groups did *not* differ on SCR amplitude for the Correct Withhold condition [F (1,71) = 2.139, $p > 0.05$], but for Aware Errors [F (4,58) = 4.047, $p < 0.01$]. Bonferroni-corrected post-hoc comparisons revealed that right frontal lesion patients showed significantly attenuated SCR amplitudes to aware errors compared to controls ($p < 0.05$). Mean SCR amplitudes for correct withholds and aware errors in each group are displayed in Figure 3.6 below.

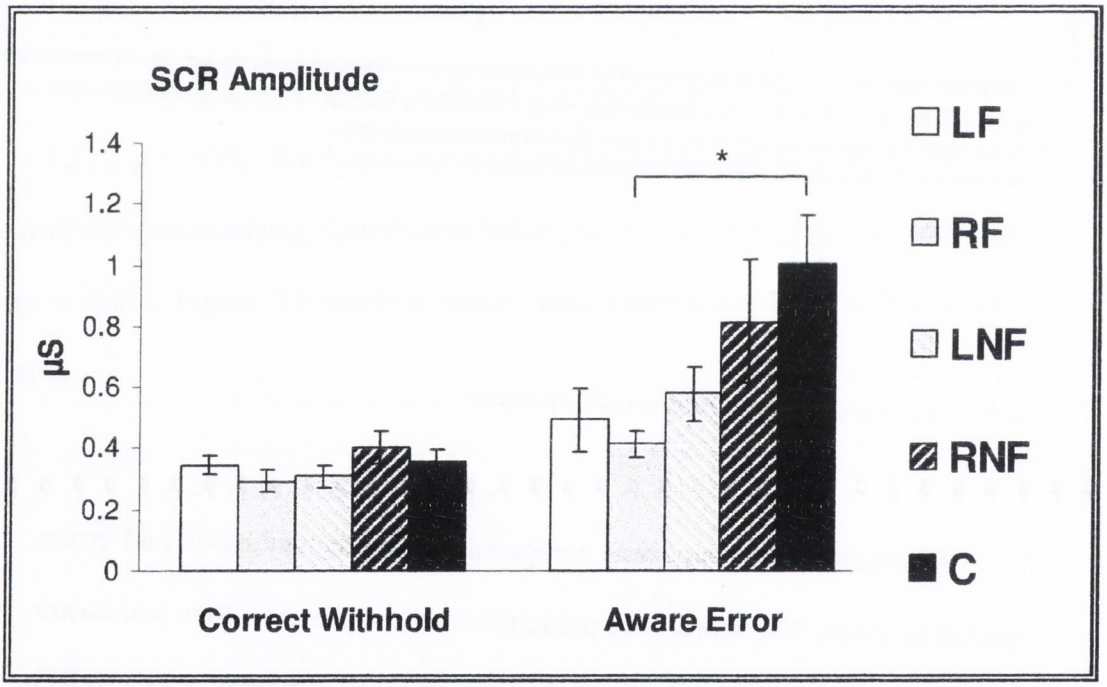


Figure 3.6 SCR Amplitude for Correct Withholds and Aware Errors for all Groups. While no group differences existed on correct withholds, RF lesion patients showed attenuated SCR amplitudes to aware errors.
Note: Error bars denote the standard error of the mean. * $p < 0.05$.

3.3.7 Accuracy during Estimation Tasks - Anticipatory and Emergent Online Awareness

Mean accuracy was calculated for participants' performance estimate *before task completion* (anticipatory awareness) and *after task completion* (emergent awareness) on six cognitive tasks (Digit Span Forward, Digit Span Backward, Spatial Span Forward, Spatial Span Backward, Verbal Fluency and Category Fluency) (Prediction / Performance X 100). A value of 100 indicates perfect accuracy, while values larger and smaller than 100 indicate over-estimation and under-estimation, respectively. A mixed ANOVA with Accuracy Condition (2 levels: Accuracy *Before* and Accuracy *After Task Completion*) as Within-Subjects factor and Group (5 levels: RF, LF, LNF, RNF and C) as between-subjects factor, was performed. A significant main effect of Group emerged [$F(4,71) = 2.666$, $p < 0.05$], while the main effect of Accuracy Condition approached significance [$F(1, 71) = 3.804$, $p = 0.055$]. No significant Group by Accuracy Condition was observed [$F(4, 71) = 0.465$, $p > 0.05$]. Bonferroni pairwise comparisons showed that across all groups, mean accuracy *before task completion* lay at 91.85 %, while *after task completion*, it was significantly lower at 81.26 % ($p < 0.05$), suggesting that all groups under-estimated their performance, and further adjusted their estimates downward after task completion. Across conditions, LF patients differed significantly from controls ($p < 0.01$), with accuracy scores suggesting that LF patients over-estimated their cognitive performance, while controls tended to under-estimate how well they would perform. Figure 3.7 shows mean accuracy scores before and after task completion, and illustrates how LF lesion patients over-estimated

their performance prior to task begin, while after task completion, performance estimates fell below 100.

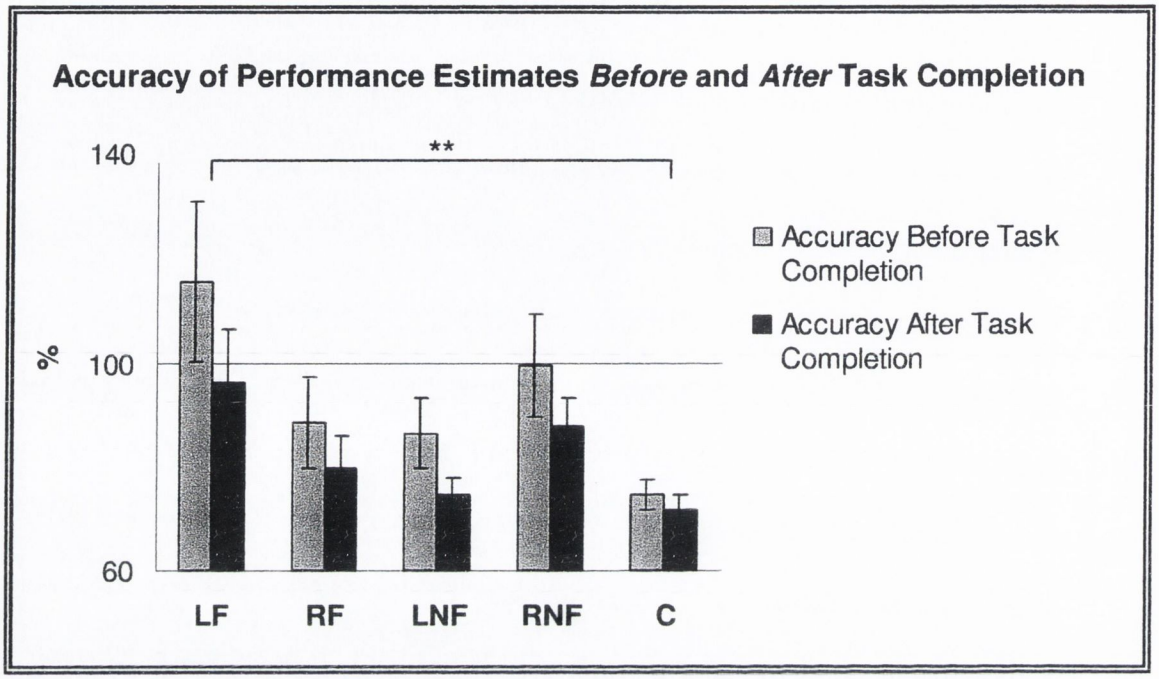


Figure 3.7 Mean Accuracy Scores *Before and After Task Completion* for all Groups. Scores reflect the combined accuracy on Digit Span, Spatial Span, Verbal and Category Fluency Tasks. Scores of less than 100 indicate under-estimation, while scores above 100 indicate over-estimation. Notably, LF lesion patients over-estimated their cognitive performance prior to task begin, but adjusted their estimate afterwards. All other groups under-estimated how well they would perform before task begin, and provided even more conservative estimates after performing the task.
Note: ** $p < 0.01$. Error bars denote the standard error of the mean.

3.3.8 Relationship between Time Since Lesion and Awareness Measures among Patients

In order to investigate whether a relationship existed between the time since lesion and all awareness measures, partial correlations were performed across all patients (N = 57), controlling for the effect of patient group. Time Since

Lesion did not correlate with Metacognitive Awareness, Online Emergent Awareness during SART or Online Anticipatory Awareness (Performance Estimate Before Task Completion) scores (all df = 53; all $p > 0.05$).

3.3.9 Relationship between Awareness Measures, Sustained Attention and Measures of 'Frontal Systems' Function across all Participants

Partial correlations were computed across all participants (controlling for the effect of group) in order to examine the relationship between awareness scores (metacognitive, anticipatory and online emergent) and measures of frontal lobe functioning. Thus, the variables entered into the correlation matrix were Metacognitive Awareness, Anticipatory Awareness (Performance Estimate Before Task Completion), Online Emergent Awareness (error awareness during SART), SART commission errors, Verbal & Category fluency, SOPT errors and FrSBe (Other) scores.

Metacognitive awareness correlated negatively with SART commission errors ($r = -.237$, df = 72, $p < 0.05$) and FrSBe (Other) scores ($r = -.403$, df = 72, $p < 0.01$). The positive correlation between metacognitive awareness and verbal fluency fell just short of statistical significance ($r = .221$, df = 72, $p = 0.059$). Anticipatory awareness scores, correlated positively with SART commission errors ($r = .279$, df = 72, $p < 0.05$) and FrSBe (Other) scores ($r = .255$, df = 72, $p < 0.05$), suggesting that those who over-estimated their cognitive performance also made more SART errors and were rated as showing more

FrSBe symptoms. The correlation between anticipatory awareness scores and SOPT errors approached significance ($r = .220$, $df = 72$, $p = 0.059$), suggesting that over-estimation of cognitive performance was also associated with more errors on the SOPT. Furthermore, over-estimation of cognitive performance was associated with lower verbal fluency ($r = -.395$, $df = 72$, $p < 0.01$) and category fluency scores ($r = -.485$, $df = 72$, $p < 0.01$).

Online emergent awareness of errors during SART did not correlate with any other measure (all $p > 0.05$).

Table 3.4 displays the partial correlation coefficients for all correlations performed.

Table 3.4. Partial Correlation Coefficients for Relationships Between Awareness Measures, Sustained Attention and 'Frontal Systems' Measures.

	Metacognitive Awareness	Anticipatory Awareness	Online Emergent Awareness
SART Commission Errors	-.237*	.279*	-.213
Verbal Fluency	.221	-.395**	.019
Category Fluency	.144	-.485**	.115
SOPT Errors	.054	.220	-.029
FrSBe (Other) Total Score	-.403**	.255	-.058

* $p < 0.05$; ** $p < 0.01$, uncorrected for multiple comparisons

3.3.10 Functional Relationships Between Awareness Measures

In order to examine the functional relationship between metacognitive, anticipatory and online emergent awareness, partial correlations were

performed, with the effect of group controlled for. This analysis revealed that metacognitive awareness was not associated with online emergent awareness ($p > 0.05$). However, a significant, though relatively weak, negative relationship emerged between metacognitive and anticipatory awareness, indicating that those participants who over-estimated their performance on estimation tasks also showed poor metacognitive awareness scores ($r = .241$, $df = 72$, $p < 0.05$).

3.4 Discussion

The current study aimed to investigate the neural correlates of self-awareness by assessing the effects of focal cortical lesions on a number of measures self-awareness. Specifically, metacognitive and online awareness were investigated in unilateral prefrontal lesion patients, as well as patients with unilateral lesions outside the frontal lobe.

The questionnaire data showed that both left and right frontal lesion patients under-estimated their difficulties, as well as the extent of their change in behaviour since injury, and thus exhibited impaired metacognitive awareness. This lends support to neuroanatomical/neurocognitive models which have posited self-awareness and insight as the highest cognitive function of the frontal lobes (e.g. Stuss, 1991; Stuss, Floden, Alexander, Levine, & Katz, 2001). Additionally, online emergent awareness was measured, by asking patients to monitor their performance during a simple task of sustained attention, and indicate their error awareness. RF lesion patients showed significantly lower error awareness compared to healthy controls, which was accompanied by a decreased autonomic skin conductance response (SCR) to errors reported as aware. This suggests that one possible mechanism accounting for self-awareness impairments following frontal lobe damage may be a deficit in error monitoring, mediated by lowered autonomic arousal, for which right prefrontal cortex functioning is crucial. Neuroimaging results such as those of Beauregard, Levesque, & Bourgouin (2001) have shown that right prefrontal cortex plays a prominent role in the regulation of autonomic nervous

system function. More specifically, Zahn, Grafman, & Tranel (1999) have demonstrated that right prefrontal cortex lesions impair the generation of SCRs to psychologically significant stimuli, rather than impairing SCRs per se. Previous studies have also shown that among TBI patients, a specific deficit exists in generating an arousal response to errors, as indexed by lowered SCR amplitudes, which suggests that a link exists between autonomic arousal and error awareness (O'Keeffe et al., 2004).

This proposal of a specific error-monitoring deficit among RF lesion patients is further strengthened by the results of the accuracy scores on the performance estimates tasks. As a measure of anticipatory awareness, participants were asked to estimate their performance on simple cognitive tasks such as digit span and verbal fluency. Although LF lesion patients initially over-estimated how well they could perform, upon completion of the task, they adjusted their estimate to very conservative judgments, which suggests that their online emergent awareness was unimpaired. LF lesion patients showed the largest magnitude of adjustment following task completion, while RF lesion patients made smaller adjustments than any other patient group. It is noteworthy, however, that RF lesion patients did not initially over-estimate, and thus cannot be said to exhibit impaired anticipatory awareness. Anticipatory awareness is likely to vary with the specific task demand (Toglia & Kirk, 2000) and likely to draw on a range of cognitive subprocesses, including memory and language, for which the current sample of LF lesion patients showed poorer performance than controls. Thus, while left prefrontal cortex may play an important role in giving rise to accurate anticipatory awareness, further studies are required to validate such neuroanatomical specificity. A firm conclusion from the present

study remains, however, that for left frontal lesion patients, erroneous responses reached awareness during task performance, both during SART and cognitive estimation tasks. Such online emergence of error awareness was impaired among right prefrontal lesion patients, when compared with controls.

To further examine of the role of the frontal lobes for self-awareness, partial correlation coefficients among measures of frontal lobe functioning (sustained attention, executive functions and FrSBe ratings for symptoms of frontal dysfunction) and awareness categories (metacognitive awareness, online emergent and online anticipatory awareness), were computed. Metacognitive awareness was associated with fewer SART commission errors, and thus better sustained attention ability, which was also the case among the sample of healthy young adults reported in Chapter 2 (Hoerold et al., 2008). Metacognitive awareness was also associated with lower symptoms of frontal systems dysfunction, as indexed by FrSBe (Other) ratings, which has also been shown among TBI patients (O'Keeffe, Dockree et al., 2007) and degenerative illness with abnormal tau protein levels (O'Keeffe, Murray et al., 2007). These findings, combined with the current results of impaired self-awareness among both frontal lesion patient groups, further strengthen the models that associate metacognitive self-awareness with frontal-striatal regions. Anticipatory awareness, on the other hand, was associated with sustained attention errors and verbal and category fluency, which stands in contrast with the results of O'Keeffe, Murray et al. (2007) and partially with the TBI findings of O'Keeffe, Dockree et al. (2007), who reported sustained attention failures, but not fluency performance to be important. As previously mentioned, however, cross-study

comparisons are difficult to make since widespread damage may account for the findings of O'Keeffe and colleagues. Of note, Time Since Lesion (TSL) was not associated with any of the awareness measures, which is most likely due to the fact that all patients were non-acute cases, tested at least 6 months post-injury.

In conclusion, right prefrontal lesion patients display both poor metacognitive awareness *and* poor online emergent awareness of errors, while left prefrontal lesion patients show poor metacognitive awareness but intact emergent error awareness. It is possible that among left prefrontal lesion patients, poor memory performance may have contributed to their lowered metacognitive awareness, while for right prefrontal lesion patients, a likely mechanism to account for impairment is an error monitoring deficit. This may be part of a more general monitoring deficit, as has been proposed to account for cases of persistent anosognosia, where right prefrontal hypoperfusion was also present (Venneri & Shanks, 2004). Such a deficit may in turn be mediated by their decreased ability to self-sustain a sufficient level of autonomic arousal, as our SCR results suggest. On neuropsychological performance, these right prefrontal patients showed no discernable impairment, except for delayed recall of faces. This links in with a widely acknowledged view of right prefrontal lesion patients exhibiting minimal impairment on standard neuropsychological assessment. Future studies should examine the role of task difficulty on awareness processes, since LF lesion patients in the current study showed most impairment on neuropsychological tasks, the experience of which may itself have contributed to their emerging awareness. Self-awareness impairments

represent significant challenges for caregivers, family members and clinicians, and deficits in error monitoring can be targeted for rehabilitation (see McAvinue et al., 2005). Therefore more systematic research on the factors which give rise to error awareness is required, allowing rehabilitation professionals to make optimal use of findings such as those of the present study. Additionally, it must be borne in mind that the effects reported in this study do not show double dissociations between patient groups. Rather, the results show that individual patient groups differed statistically from healthy controls. Thus, future studies should further investigate to what extent patients differ from each other in performance of these tasks, and their awareness of them.

Chapter 4 : Electrophysiological Correlates of Error Awareness in Focal Lesion Patients

Abstract

The current study aimed to examine the effects of frontal and non-frontal cortical lesions on electrophysiological correlates of error detection. The error-related negativity (ERN or Error Negativity, Ne) and the Error Positivity (Pe) are two ERP components thought to reflect separate aspects of error monitoring, with increasing evidence that the Pe, rather than the ERN, may be linked with the processes reflecting conscious awareness of erroneous performance. Twelve frontal and 13 non-frontal cortex lesion patients completed a task specifically designed to extract an error awareness score, and elicit these ERP components from aware error trials. Behaviourally, groups did not differ on error rates, but non-frontal lesion patients showed lowest overall awareness scores on the task. While controls exhibited a clear ERN following errors and a smaller negative deflection on correct trials, frontal lesion patients failed to show the electrophysiological difference between correct and erroneous responses. Non-frontal lesion patients, by contrast, showed a significantly reduced Pe, suggesting a change in processing of aware errors. The findings further suggest that error awareness may involve posterior cortical areas, depending on individual task characteristics.

4.1 Introduction

4.1.1 Brief Overview of Electrophysiological Measures

Electroencephalography (EEG), the use of a set of electrodes on the scalp to measure changes in electrical brain activity, was first described by Hans Berger in 1929 (Berger, 1929). Specifically, the EEG maps voltage changes caused by changing polarisation of neuronal membranes. Since Berger's early reports, the relatively coarse measurement of overall brain activity has been refined; more and more attention has been directed at identifying neural traces within the EEG reading, which can be linked to specific sensory, cognitive and motor events. These can be extracted from a continuous EEG recording, typically by averaging a number of EEG segments (epochs) which contain the specific event in question. Accordingly, these phase-locked and averaged segments are referred to as Event-Related Potentials (ERPs) (Vaughan, 1969), which provide us with a measure of the "neural activity that is generated in a given neuroanatomical module when a specific computational operation is performed" (Luck, 2005, p. 59). ERPs contain a number of components in the form of positive and negative voltage deflections, the peaks of which are sometimes labelled according to polarity and time at which they occur, while others are named after the specific event with which they are associated. Since this event can either be an external stimulus presented to the participant *or* a particular response made by the participant, a broad distinction is often drawn between *stimulus-locked* ERPs and *response-locked* ERPs. In both cases, the most common measurements are amplitudes and latency of the ERP

component in question, varying either between conditions or between particular participant groups. Today's electrophysiological recording techniques allow measurement of component latency in the range of milliseconds, making ERPs an attractive research tool for anybody interested in the timing of neural processes. In comparison with other techniques such as Positron Emission Tomography (PET) and functional Magnetic Resonance Imaging (fMRI), the ERP method provides relatively poor spatial resolution, due to the infinitely large combination of underlying neural generators that can lead to an observed voltage distribution on the scalp (the 'inverse problem'). However, in recent years, source localization techniques have become increasingly sophisticated, EEG channels can be applied at an increasingly high density, and the co-registration of EEG and neuroimaging signals is becoming a viable means to attenuate this problem. Thus, the presence, absence, amplitude and timing of these phase-locked EEG signals can contribute significantly to our understanding of specific neurocognitive processes, and will be utilized in this chapter to investigate the neural correlates of error awareness in focal cortical lesion patients and healthy control participants.

4.1.2 ERPs Related to Cognitive Control and Performance Errors

As outlined above, ERPs can be phase-locked to a given *stimulus*, or to a particular *response* executed by the participant during a task, thereby allowing the study of the cognitive processes associated with that response. In the

context of action monitoring paradigms, two ERP components related to the processing of erroneous responses have attracted much interest over the past 15 years. The first component, the error-related negativity (ERN, sometimes referred to as error negativity, Ne), was first described by two research groups independently during the early 1990s (Falkenstein, Hohnsbein, Hoormann, & Blanke, 1991; Gehring, Goss, Coles, Meyer, & Donchin, 1993). The ERN is most commonly observed over fronto-central channels, peaking between 50 and 150ms after the error has occurred, and has consistently been shown to generate from activity in the caudal ACC (Dehaene, Posner, & Tucker, 1994; Herrmann, Rommler, Ehlis, Heidrich, & Fallgatter, 2004; O'Connell et al., 2007; van Boxtel, van der Molen, & Jennings, 2005; Van Veen & Carter, 2002b). The second component, a lower frequency waveform known as the error positivity (Pe; Falkenstein et al., 1991; Falkenstein, Hoormann, Christ, & Hohnsbein, 2000), has a more posterior, centro-parietal scalp distribution, and occurs 200 - 500ms after the error.

The ERN has been examined under a range of experimental conditions, primarily due to its robust occurrence in simple cognitive paradigms such as go/no-go and other reaction time tasks, irrespective of motor output modality (Falkenstein et al., 2000; Holroyd, Dien, & Coles, 1998). What has emerged from this literature is a small number similar but competing accounts of the precise functional significance of this signal, the debate about which is currently ongoing (van Veen & Carter, 2006). The original proposal saw the ERN as a specific electrophysiological response to incorrectly executed actions, whereby the negative signal reflected a mismatch between the

representation of the intended (correct) and the actual (incorrect) performed action (Falkenstein et al., 1991; Scheffers, Coles, Bernstein, Gehring, & Donchin, 1996). The occurrence of an ERN-like negative deflection following correct trials, sometimes referred to as *correct*-related negativity (CRN; Vidal, Burle, Bonnet, Grapperon, & Hasbroucq, 2003; Vidal, Hasbroucq, Grapperon, & Bonnet, 2000), has led to the suggestion that the observed negativities may signal conflict between competing responses, rather than errors themselves (van Veen & Carter, 2002a). This hypothesis is further supported by computational neural network simulations (Botvinick, Braver, Barch, Carter, & Cohen, 2001; Yeung & Cohen, 2006), and accounts for many findings since most errors are probably a consequence of poorly-resolved response conflict. However, some recent studies have explicitly manipulated the degree of response conflict, and failed to demonstrate a clear role of the ERN as a conflict monitor (Burle, Roger, Allain, Vidal, & Hasbroucq, 2008; Masaki, Falkenstein, Sturmer, Pinkpank, & Sommer, 2007). Alternative theories regarding the function of the ERN focus on the likelihood of reward and favourable performance outcome, postulating that the ERN arises out of phasic changes in mesofrontal/mesolimbic dopamine activity due to changing environmental demands (Holroyd & Coles, 2002, 2008).

Although these accounts currently compete in the literature, they converge on a view of the ERN as a crucial and relatively rapid neurophysiological process embedded in a wider performance monitoring network encompassing the caudal ACC and other medial frontal structures - specifically the rostral cingulate zone (RCZ) - tightly coupled with lateral prefrontal cortex (LPFC)

regions believed to implement the necessary performance adjustments (Ridderinkhof, Ullsperger, Crone, & Nieuwenhuis, 2004). Figure 4.1 provides a simplified schematic overview of the putative components of the network, as summarized by Ullsperger (2006).

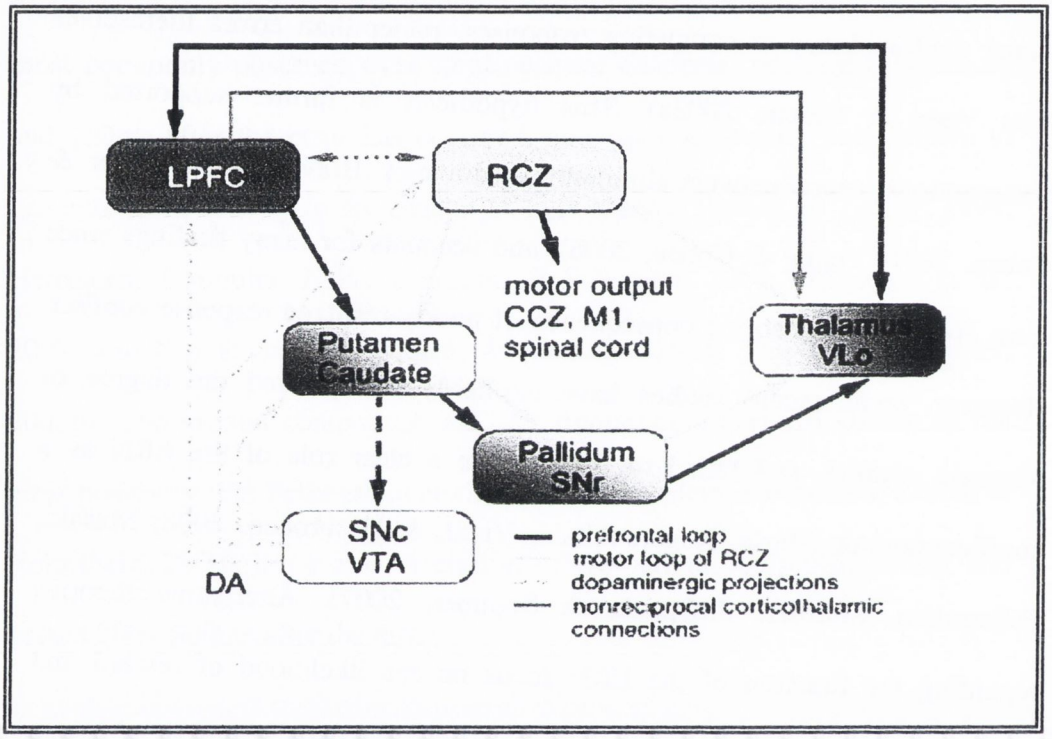


Figure 4.1. Simplified Schematic of the Performance Monitoring Network. The RCZ and LPFC are each well integrated into segregated cortico-striato-thalamo-cortical loops, which themselves interact at various stages, as for example via the non-reciprocal connection between LPFC and the thalamus (dark grey arrow). The coupling between RCZ and LPFC is shown by a dotted grey arrow.
Abbreviations: CCZ = caudal cingulate zone, DA = dopamine, LPFC = lateral prefrontal cortex, M1 = primary motor cortex, RCZ = rostral cingulate zone, SNC = substantia nigra pars compacta, SNr = substantia nigra pars reticularis, VLo = nucleus ventrolateris pars oralis of the thalamus, VTA = ventral tegmental area. From Ullsperger (2006).

In contrast to the ERN, the specific functional significance and neural source of the Pe have been investigated in fewer studies, most likely because it is less

consistently observed during performance monitoring experiments than the Pe (see Overbeek, Nieuwenhuis, & Ridderinkhof, 2005, for a review). As described earlier, the Pe emerges as a temporally and topographically distinct component from the ERN, between 200-500ms post-response, with peak amplitudes observed at more posterior midline electrode sites. Source localisation attempts have shown that this signal also emerges from an anatomically separate source than the ERN, namely the rostral ACC (Herrmann et al., 2004; van Boxtel et al., 2005; Van Veen & Carter, 2002b), though findings are slightly inconsistent. Data from O'Connell et al.'s (2007) source analysis model suggests that more posterior areas, including the precuneus, may be involved. Functionally, the Pe has been attributed a role in implementing strategic response control following errors, emotional or motivational assessment of errors, or indeed conscious awareness of errors (Falkenstein et al., 2000). Indeed, while Overbeek et al.'s (2005) meta-analysis showed little support for the strategy implementation and affective processing views of the Pe, a small number of ERP studies to date have measured error awareness explicitly, and all have found strong evidence that Pe amplitude is modulated by conscious awareness of errors (Belopolsky, Kramer, & Theeuwes, 2008; Endrass, Franke, & Kathmann, 2005; Endrass, Reuter, & Kathmann, 2007; Nieuwenhuis, Ridderinkhof, Blom, Band, & Kok, 2001; O'Connell et al., 2007). The ERN, in each case, did not differ in amplitude between aware and unaware errors, supporting the notion that it serves primarily as a non-conscious detection mechanism signalling the need for change. The Pe, in contrast, may represent the electrophysiological correlate of error awareness processes, which undoubtedly include other subcomponents,

including effortful attention, subjective significance and the mapping of somatic markers, as evidenced by findings showing a positive correlation between Pe amplitude and skin conductance response (SCR) (Hajcak, McDonald, & Simons, 2003). In this view of the functional relevance of the Pe, findings of its potential neural generators lying closer to the precuneus are no longer surprising, given the presumed role of the precuneus and other posterior/parietal cortical areas in self-awareness (Blakemore & Frith, 2003; Cavanna & Trimble, 2006). Similarly, the two fMRI studies published to date to explicitly distinguish between aware and unaware errors have both failed to showed increased activity in the ACC for awareness, but rather increased activity in bilateral pre-frontal and parietal cortex in one case (Hester et al., 2005), and left anterior inferior insula in the second case (Klein et al., 2007).

4.1.3 Error Processing in Neurological Patient Groups

A small number of studies has investigated neural correlates of error processing in neurological patients, in an effort to identify causal effects of disrupted processing pathways within the performance monitoring network outlined in Figure 4.1 above. On purely behavioural measures, Swick and colleagues (Swick & Jovanovic, 2002; Swick & Turken, 2002) have provided evidence from two rare patients with unilateral lesions to the rostral cingulate zone (RCZ), who showed contrasting performance monitoring behaviours. One patient, characterised by a right posterior RCZ lesion reaching into caudal cingulate cortex, showed unimpaired performance on incongruent trials of the

Stroop task, but failed to benefit from the facilitation effects normally observed on congruent trials. In contrast, the second patient whose lesion included the left anterior RCZ, extending superiorly towards BA 32 and BA 8, showed increased interference effects and increased error rates on incongruent Stroop trials (Swick & Jovanovic, 2002). The ERP findings from this patient showed that negative amplitudes for errors and correct responses did not differ (Swick & Turken, 2002), suggesting that left anterior RCZ lesions may abolish error-specific signals, leaving more general performance processing signals intact. Stemmer, Segalowitz, Witzke, & Schonle (2004) have reported ERP results from five patients with bilateral lesions of the anterior mesial frontal cortex, and found both the ERN and the Pe to be attenuated in four of those patients. Interestingly, one patient, whose lesion was described as less extensive on the left side, *did* produced a relatively unimpaired ERN and Pe, corroborating findings from Swick & Turken's single case study. In contrast to these studies, Fellows & Farah (2005) have presented four patients with extensive lesions involving large parts of the RCZ, who showed neither significantly increased error rates on the Stroop task, nor an impairment in performance adjustments, challenging a view of the necessity of RCZ areas in cognitive control. Furthermore, lesions to the LPFC (Gehring & Knight, 2000; Ullsperger, von Cramon, & Muller, 2002), and focal lesions to the basal ganglia have also been shown to abolish the difference in amplitude between errors and correct responses (Ullsperger & von Cramon, 2006), which suggests that the ACC may not be the only crucial structure in the generation of an error-specific ERN. The Pe was also found to be attenuated in LPFC and basal ganglia patients (Ullsperger & von Cramon, 2006; Ullsperger et al., 2002), while frontopolar as

well as temporal lesions did not affect the Pe (Ullsperger et al., 2002). Importantly, however, none of these lesion studies explicitly measured error awareness, which, as discussed previously, modulates the amplitude of the Pe. Stemmer and colleagues observed patients during task performance, and described that some patients showed error awareness through grimacing and exclamations, but no awareness score could be provided. During the recording of an EEG experiment, participants are usually required to minimize unnecessary movement, thus error awareness must be assessed via a secondary response to indicate errors, embedded in the task. This allows an analysis of electrophysiological correlates of performance errors without a possible contamination from awareness differences across one individual's session.

4.1.4 Current Study

The current study aimed to investigate the electrophysiological correlates of error processing, with specific emphasis on conscious error awareness, in a sample of focal frontal and non-frontal lesion patients, in an effort to replicate and extend previous findings. The ERN has been found to be attenuated in a number of patients with lesions localised to the frontal lobe (Gehring & Knight, 2000; Stemmer et al., 2004; Swick & Turken, 2002; Ullsperger & von Cramon, 2006; Ullsperger et al., 2002), therefore similar findings are expected from the current study. Inconsistent findings exist with respect to the Pe, with some reports showing an attenuating effect of frontolateral lesions (Ullsperger & von Cramon, 2006; Ullsperger et al., 2002), but not of bifrontopolar lesions

(Ullsperger et al., 2002) or bilateral MFC lesions (Stemmer et al., 2004). If the Pe is indeed a correlate of error awareness, then such inconsistencies could arguably have arisen from differences in patients' awareness rates. Thus, the present study explicitly measured error awareness, and aimed to examine three ERP components relevant to performance monitoring processes: The CRN following correct trials, and the ERN and Pe following erroneous responses.

4.2 Method

4.2.1 Participants

All patients recruited for this experiment were selected from the cohort of patients already recruited from Beaumont Hospital, Dublin, for the study reported in Chapter 3. Consequently, all recruitment, diagnosis and consent procedures are equivalent to those of the previous chapter. The research was approved by the research ethics committee boards of Beaumont Hospital, Dublin, and the School of Psychology, Trinity College Dublin.

For the purpose of the current study, three groups of participants were examined:

1. a group of 12 patients diagnosed with a unilateral focal lesion in ***frontal*** cortex (excluding motor cortex) (7 male, 5 female; 11 right-handed, 1 left-handed; mean age 46.7 years, range 23-62 years; mean years of education 15.6 years, range 10-22; mean Time Since Lesion = 61.4 months);
2. a group of 13 patients diagnosed with a focal unilateral ***non-frontal*** cortical lesion (9 male, 4 female; 10 right-handed, 3 left-handed; mean age 45.5 years, range 27-67; mean years of education 15.4 years, range 8-26; mean Time Since Lesion = 58.5 months);

3. a control group of 15 volunteer participants with no history of neurological, psychiatric or psychological disorder (7 males, 8 females; 12 right-handed, 3 left-handed; mean age 47.5years, range 23-67; mean years of education 17.5 years, range 14-22).

Clinical information for each patient is provided in Table 4.1 below. As indicated, some clinical scans were unavailable, however consultants' lesion descriptions are provided for all patients. 'Y' indicates that the patients' EEG data were included in the ERP analysis, 'N' indicates that EEG data were excluded due to insufficient number of errors , i.e. < 15. Time Since Lesion (TSL) did not differ between frontal and non-frontal lesion patients [$t = 0.152$, $df = 23$, $p > 0.05$].

MRI/CT images for the patients in this study are provided in Figure 4.2a-b.

Table 4.1. Clinical Data for Patients.

Patient ID	Diagnosis	Side of Lesion	TSL (Months)	Neuro-Imaging	ERP Analysis
	Frontal Lesion Group				
008 OC	Grade III Glioma	L	65	CT	Y
016 MF	Anaplastic Glioma	L	36	MRI	Y
021 PH	Medial FL Aneurysm (Clipped)	R	30	CT	Y
115 BD	Contusion (HI)	L	91	CT	N
169 JW	Subdural Abscess	R	160	N.A.	Y
216 AMC	AVM with Associated Haemorrhage	R	125	N.A.	Y
239 BM	Lacunar Infarct	L	86	CT	N
335 JB	Grade II Glioma	R	24	MRI	Y
346 PF	Grade III Glioma (Debulked)	R	33	N.A.	Y
348 RS	Grade II Glioma	L	47	MRI	Y
360 JOR	Grade I Meningioma	L	17	MRI	Y
363 BMG	ACA Aneurysm (Coiled)	L	23	MRI	Y
	Non-Frontal Lesion Group				
002 CFB	Parieto-Occipital AVM	L	94	MRI	Y
046 AB	MCA Territory Non-Haemorrhagic Infarction	R	20	CT	Y
088 WB	Parietal Skull Fracture (HI)	R	134	CT	Y
162 PH	PCA aneurysm (Clipped)	R	118	CT	Y
166 JC	Temporo-Occipital Subdural Haematoma	L	74	CT	Y
334 MU	Focal Posterior Parieto-Occipital Cortical Atrophy	L	144	MRI	Y
336 PC	Occipital Haemorrhage due to Suspected AVM	L	17	CT	Y
337 CC	Temporal Lobe AVM (Excised)	R	10	CT	Y
339 MF	Hippocampal Sclerosis (Hippocampectomy)	L	55	MRI	N
343 GF	Hippocampal Sclerosis (Hippocampectomy)	R	28	MRI	Y
345 AP	Parieto-Occipital AVM with Associated Haemorrhage	L	11	MRI	N
347 AA	PCA aneurysm (Coiled)	L	20	CT	Y
349 MON	Mesial Temporal Sclerosis	R	36	MRI	N

Note: ACA = Anterior Cerebral Artery; AVM = Anteriovenous malformation; CT = Computerized Tomography; HI = Head Injury; MCA = Middle Cerebral Artery; MRI = Magnetic Resonance Imaging; N.A. = Not Available; PCA = Posterior Communicating Artery; TSL = Time Since Lesion.

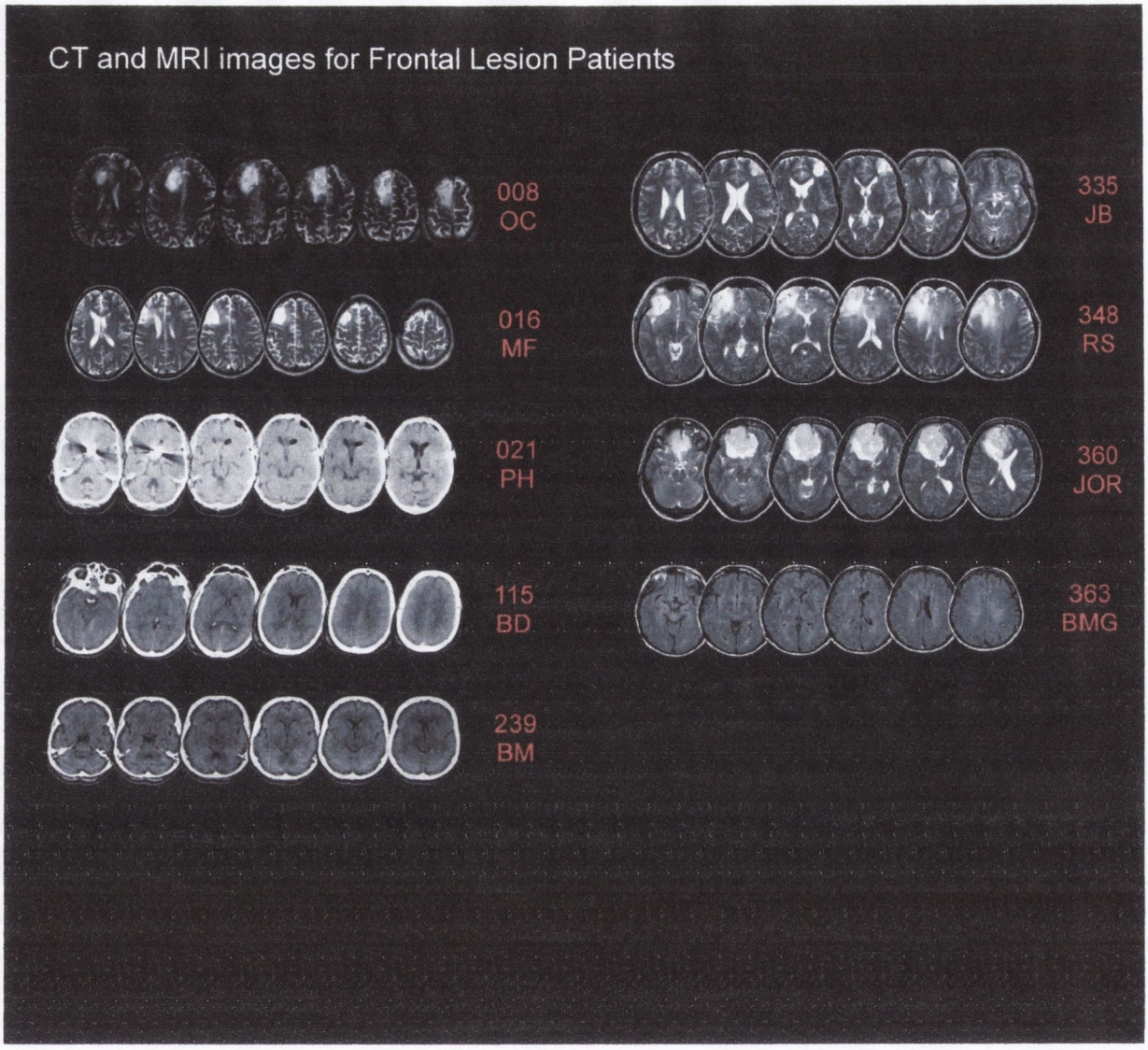


Figure 4.2a. Clinical CT and MRI Images for Frontal Lesion Patients.

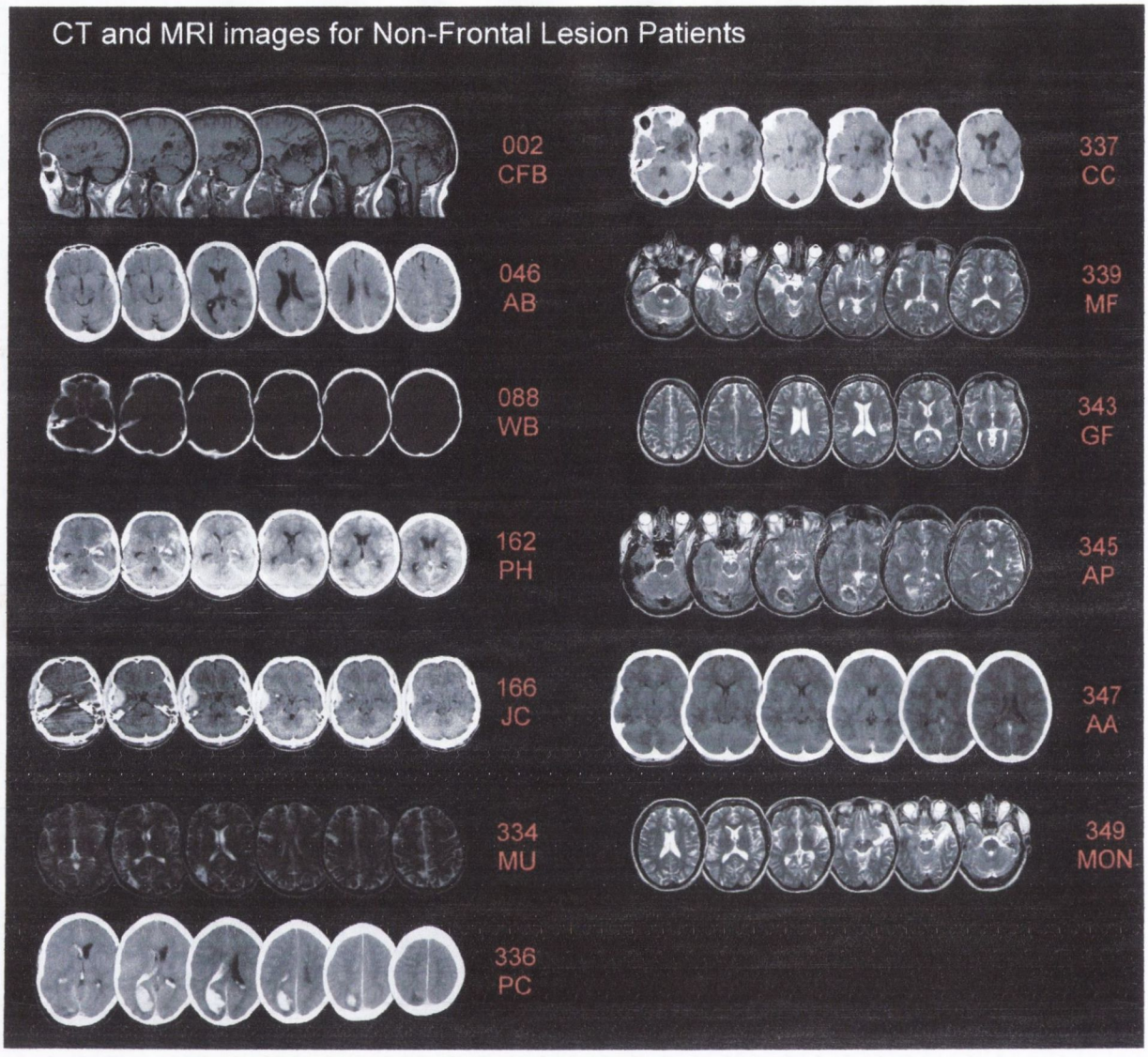


Figure 4.2b. Clinical CT and MRI Images for Non-Frontal Lesion Patients.

4.2.2 Neuropsychological Characterisation

All participants had previously undergone neuropsychological assessment, as detailed in Sections 3.2.2.1 and 3.2.2.2 of Chapter 3.

4.2.3 Questionnaire Data

As described in Section 3.2.2.3 of the previous chapter, participants were rated by their significant others for everyday cognitive failures on the Cognitive Failures Questionnaire (CFQ-Other), symptoms of frontal systems dysfunction on the Frontal Systems Behavior Scale (FrSBe-Other) and real-life competencies on the Patient Competency Rating Scale (PCRS-Other).

4.2.4 Error Awareness Task (EAT; Hester et al., 2005; O'Connell et al., 2007)

Participants completed between 4 and 8 blocks of a simple go/no-go task specifically developed to investigate error awareness [Error Awareness Task (EAT); Hester et al., 2005; O'Connell et al, 2007; see Figure 4.3], which has previously been shown to elicit the error-related ERP components of interest (O'Connell et al., 2007). In this task, go-stimuli consist of congruent colour words (matching word and font colour), while no-go stimuli consist of incongruent colour words (word and font colour do *not* match) or repeat colour

words (the same word and colour appear on two consecutive trials). No-go stimuli were randomly embedded in the sequence, and occurred in 11.1 % of cases, such that 25 stimuli in each block were no-go targets (13 repeat, 12 incongruent stimuli per block). Six colours were used (white, yellow, green, blue, purple and red), and presented in 64pt font on a grey background, in the centre of a 16" by 12" monitor. All stimuli were presented at a distance of approximately 100cm, for 600msec followed by a 900msec ISI, and appeared 0.25° above a white fixation cross. Participants were instructed to focus on the fixation cross in order to minimize eye movements.

Participants used their right thumb to press the 'Go' button on a game pad, and were required to withhold button presses for no-go stimuli. Speed and accuracy were equally emphasized. Three short practice blocks were administered to each participant, in which they were also trained to indicate awareness of a commission error by pressing a separate, adjacent button on the trial *following* the error, so that signals related to erroneous responses and signals related to indicating an error would be temporally separated. Note that only errors which participants reported as *aware* in this manner were included in the ERP analyses, which compared ERP components related to correct go-trial responses and aware commission errors. Behavioural variables extracted included % errors and % error awareness, variability of go-trial RTs (defined as the standard deviation of go-trial RTs), and % go-trial omissions.

Experimental sessions took place in a dimly-lit room, free from auditory or other distractions, and did not exceed 2 hours, including all set-up procedures and sufficient rest between blocks.

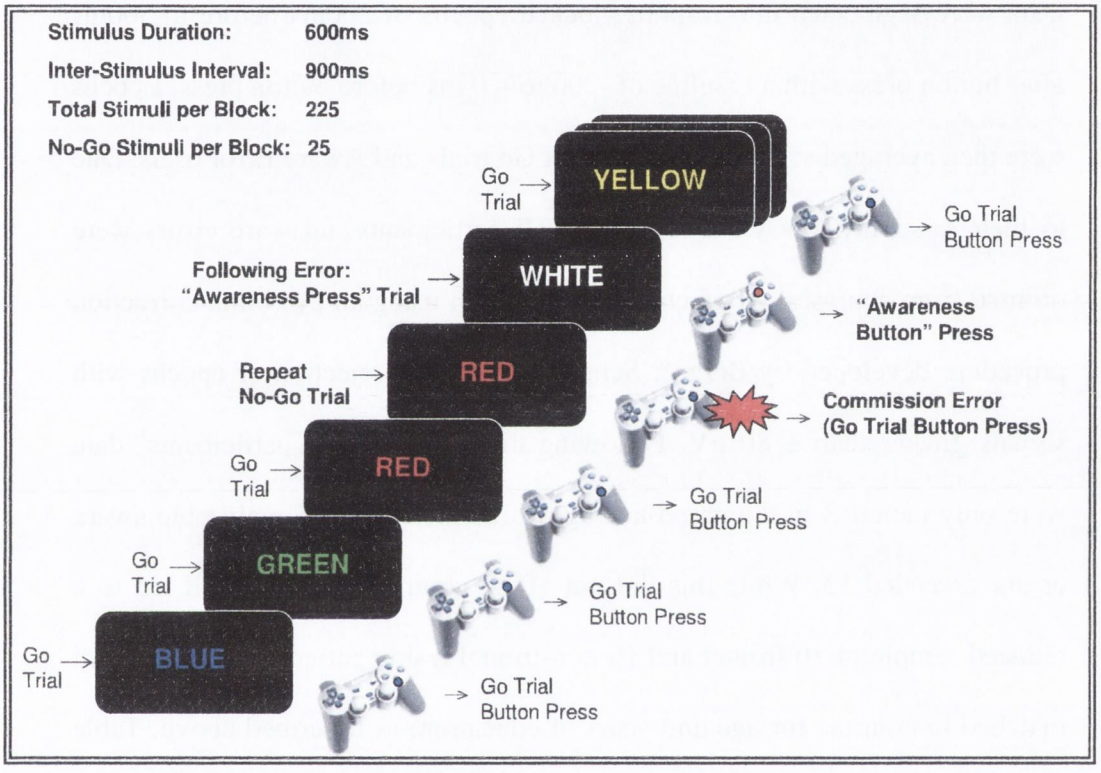


Figure 4.3. Example of an Error during the Error Awareness Task (EAT). Shows an example of a "repeat-type" error, and its subsequent indication as an *aware* error on the next trial. All participants received sufficient practice with this procedure before EEG recording began, and understood the task instructions well. Error-trial ERPs were only analysed if awareness was indicated in this manner.

4.2.5 EEG Data Acquisition

Continuous EEG recordings were acquired from 128 scalp electrodes, using the ActiveTwo Biosemi™ system, digitized at 512Hz. Eye movements were recorded using four EOG electrodes placed at the at the outer canthus of the

right and left eye and above and below the centre of the right eye. Data were analyzed using BESA Version 5.1 (Brain Electrical Source Analysis, MEGIS Software, Germany; www.besa.de). Data were filtered using a 35 Hz low pass (48dB/octave) filter and referenced to the average of the 128 scalp electrodes. Data were segmented into response-locked epochs of 200ms before to 500ms after button press with a baseline of -200 to – 0 ms before button press. Epochs were then averaged separately for Correct Go trials and Aware Error trials. Due to their relatively low yield for almost all participants, unaware errors were omitted from analyses. Artefacts were dealt with using an eye blink correction procedure developed by Berg & Scherg (1994), and rejection of epochs with signals greater than ± 80 μV. Following these procedures, participants' data were only included in the grand-averages if their number of analyzable aware errors exceeded 15. While this did not affect control participants, it led to a reduced sample of 10 frontal and 10 non-frontal lesion patients, who were still matched to controls for age and years of education, as described above. Table 4.1 indicates which patients were included in the ERP analyses. The mean number of error segments included ranged from 15 to 102, with no statistical difference between groups [$F < 1$, $p > 0.05$; mean error segments - controls = 47.0 (SD 30.4), frontal lesion patients = 35.1 (SD= 26.4), non-frontal lesion patients = 42.2 (SD=27.9)].

4.2.6 Definition and Analysis of ERP Components

A first inspection of control participants' grand-average ERPs showed a negative deflection peaking approximately 85ms after erroneous responses along the central midline, with maximal amplitude at Fz, with minimal variation between participants, and in accordance with previous reports of error-related ERP components. The ERN was therefore defined as the largest negative peak between 0 ms and 150 ms at FCz, Fz, or Cz, to allow for potential variation among patients. The grand-average also showed the Pe emerging as a clear peak around 310ms, maximal at Cz, and was therefore defined as the largest positive peak at Fz, Cz or CPz between 200 ms and 500 ms.

4.3 Results

4.3.1 Demographic, Screening and Neuropsychological Results

Table 4.2 displays demographic, screening and neuropsychological characteristics for all groups. Groups were matched for gender ($\chi^2 = 1.456$, df = 2, $p > 0.05$), and separate univariate ANOVAs showed that groups did not differ in terms of age [$F(2, 37) = 0.102$; $p > 0.05$] , years of education [$F(2, 37) = 1.512$, $p > 0.05$] or WMS orientation score [$F(2, 37) = 0.901$, $p > 0.05$]. A group effect emerged for NART-IQ [$F(2, 37) = 7.454$, $p < 0.01$], and Bonferroni comparisons showed that non-frontal lesion patients had lower premorbid IQ scores than both controls and frontal lesion patients (both $p < 0.05$). Subsequent analyses were therefore conducted with the effect of premorbid IQ covaried.

All participants scored above the cut-off score for impairment on the Frenchay Aphasia screening, VOSP shape detection or Bell's Test for neglect. Univariate ANOVAs showed no group differences on HADS anxiety [$F(2, 36) = 0.368$, $p > 0.05$] or depression scores [$F(2, 36) = 2.179$, $p > 0.05$].

Neuropsychologically, groups did not differ on memory performance (all $p > 0.05$). On both visuomotor [$F(2, 36) = 3.894$, $p < 0.05$] and sustained attention [$F(2, 36) = 7.804$, $p < 0.01$], frontal lesion patients performed significantly worse than controls (both $p < 0.05$). On measures of executive function, only

the main effect of group for verbal fluency approached statistical significance ($p = 0.056$).

On questionnaire measures completed by significant others, groups did not differ significantly on CFQ [$F(2, 36) = 1.696$, $p > 0.05$] or FrSBe scores [$F(2, 36) = 3.256$, $p > 0.05$]. On PCRS scores, the ANOVA [$F(2, 36) = 3.723$, $p < 0.01$] followed by Bonferroni comparisons showed that non-frontal lesion patients were rated lower on everyday competencies than controls ($p < 0.01$).

Table 4. 2. Demographic, Screening and Neuropsychological Data for all Groups.

	Frontal Lesion Patients	Non-Frontal Lesion Patients	Controls	P-Value
Demographics & Screening				
N (m, f)	12 (7, 5)	13 (9, 4)	15 (7, 8)	0.483
Age (SD)	46.7 (10.6)	45.5 (10.8)	47.5 (13.2)	0.904
Education (Years) (SD)	15.6 (3.3)	15.4 (4.7)	17.5 (2.2)	0.234
NART-IQ (SD)	118.0 (8.0)[a]	110.2 (10.0)[ab]	120.9 (3.7)[b]	**0.002**
WMS Orientation (SD)	12.8 (0.7)	12.8 (0.6)	13.1 (0.6)	0.415
Frenchay Aphasia Screening	N. I.	N. I.	N. I.	---
VOSP Shape Detection	N. I.	N. I.	N. I.	---
Bells Test for Neglect	N. I.	N. I.	N. I.	---
HADS Anxiety (SD)	5.7 (3.6)	5.9 (3.8)	4.7 (2.6)	0.695
HADS Depression (SD)	2.4 (2.3)	4.6 (4.4)	2.5 (1.8)	0.128
Memory				
Logical Memory (% Retention) (SD)	78.2 (18.3)	81.4 (15.8)	86.4 (10.9)	0.373
Digit Span (SD)	16.8 (4.1)	17.6 (4.2)	20.4 (3.6)	0.104
Spatial Span (SD)	14.1 (3.8)	14.9 (3.6)	16.4 (2.7)	0.236
Faces (% Retention) (SD)	96.2 (5.4)	95.8 (5.3)	97.5 (3.7)	0.864
Attention				
Visuomotor -TMT (B-A) (SD)	92.3 (59.4)[c]	74.1 (30.4)	47.1 (28.5)[c]	**0.029**
Sustained – SART (Errors) (SD)	16.2 (9.0)[c]	10.9 (7.1)	5.4 (3.5)[c]	**0.002**
Executive Function				
SOPT Errors (SD)	7.4 (2.9)	8.0 (2.0)	5.5 (2.1)	0.183
Verbal Fluency (SD)	39.3 (13.2)	33.6 (12.0)	48.6 (12.2)	0.056
Category Fluency (Animals) (SD)	21.5 (9.3)	21.8 (5.6)	26.1 (4.3)	0.192
Questionnaire Measures				
CFQ (Other) (SD)	12.0 (7.0)	11.7 (6.3)	7.7 (5.6)	0.198
FrSBe (Other) (SD)	88.3 (30.8)	87.3 (23.8)	73.0 (13.4)	**0.050**
PCRS (Other) (SD)	130.4 (14.6)	121.9 (15.7)[b]	137.8 (8.0)[b]	**0.034**

Abbreviations: CFQ = Cognitive Failures Questionnaire; FrSBe Frontal Systems Behavior Scale; HADS = Hospital Anxiety and Depression Scale; NART = National Adult Reading Test; PCRS = Patient Competency Rating Scale; SART = Sustained Attention To Response Task; SOPT = Self-Ordered Pointing Task; TMT = Trail Making Test; VOSP = Visual Object and Space Perception Battery; WMS = Wechsler Memory Scale.

Notes: Post-hoc comparisons: [a] = Frontal vs Non-Frontal ($p < 0.05$)
[b] = Non-Frontal vs Control ($p < 0.05$)
[c] = Frontal vs Control ($p < 0.05$).

4.3.2 Behavioural Results

4.3.2.1 Group Differences Across all Task Blocks

A repeated-measures ANOVA with between-subject factor Group (Controls *versus* Frontal Group *versus* Non-Frontal Group) and within-subject factor RT Type (Go-Trial RT *versus* Aware Error RT) showed a main effect of RT Type [$F(1, 37) = 17.627$, $p < 0.001$], with no effect of Group [$F(2, 37) = 1.254$; $p > 0.05$] or interaction between factors [$F(2, 37) = 1.515$; $p > 0.05$]. Bonferroni pairwise comparisons showed that mean RTs for aware errors were slightly faster than mean go-trial RTs ($p < 0.001$) [mean aware errors = 456.80ms (SD 61.53); mean Go-Trials = 495.18ms (SD 61.53)].

Separate one-way ANOVAs showed that groups did not differ significantly on % commission errors [$F(2,37) = 0.256$; $p > 0.05$], however, an effect of group *did* exist for % error awareness [$F(2, 37) = 6.824$, $p < 0.01$). Bonferroni comparisons showed that non-frontal lesion patients had significantly lower error awareness than controls ($p < 0.01$). Additionally, non-frontal lesion patients showed more variable go-trial RTs during the task [$F(2, 37) = 6.868$, $p < 0.01$] (Bonferroni comparison $p < 0.05$). Lastly, a main effect of group emerged for % omissions [$F(2, 37) = 4.450$, $p < 0.05$), with Bonferroni comparisons confirming that frontal lesion patients showed a higher percentage of omissions than controls ($p < 0.05$). These effects are illustrated in Figure 4.3 below.

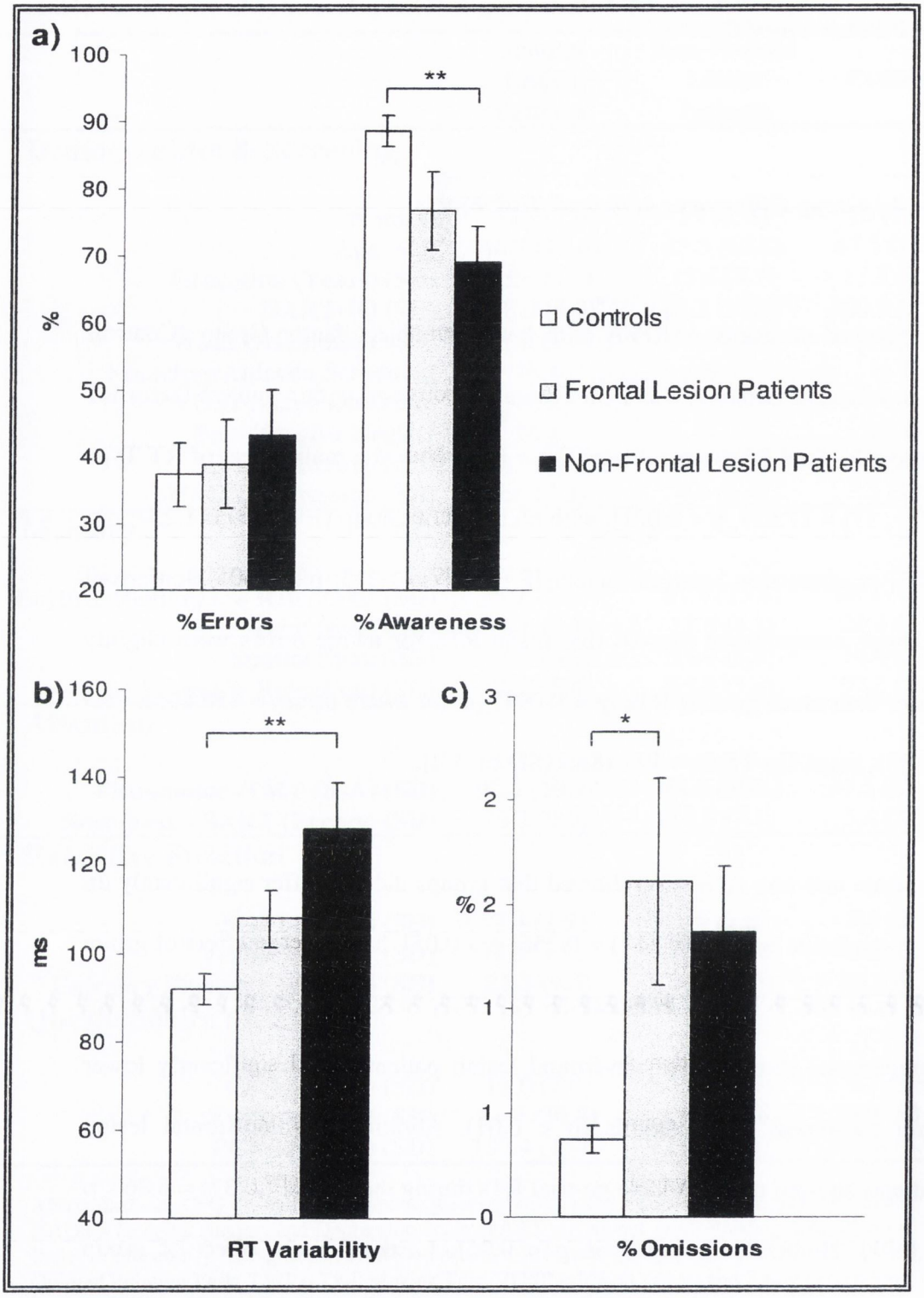


Figure 4.4. Behavioural Results for the Error Awareness Task as a Function of Group.
a) Shows that groups did not differ on error rate, but non-frontal lesion patients were significantly less aware of their errors than control participants.
b) Shows that non-frontal lesion patients showed significantly more RT variability than controls.
c) Shows that frontal lesion patients omitted significantly more go-trial targets than controls.
Error bars represent the standard errors of the mean.
* $p < 0.05$; ** $p < 0.01$

4.3.3.2 Between-Block Variation in Performance

As a measure of how much each participant varied in performance between the first four blocks of EAT[4], the standard deviation of each individual's first four mean performance values was calculated, and compared statistically between the three groups. This was done separately for EAT errors, awareness, and omissions. Separate one-way ANOVAs were performed, which showed that for EAT errors, no main effect of group existed [$F(2, 37) = 0.316$; $p > 0.05$). For awareness and omissions, groups differed significantly [awareness: $F(2, 37) = 4.905$, $p < 0.05$; omissions: $F(2, 37) = 3.528$, $p < 0.05$], with Bonferroni comparisons confirming that frontal lesion patients showed significantly more variable performance from block to block than controls (both $p < 0.05$). Table 4.3 summarises these effects, showing standard deviation values for EAT errors, awareness and omissions across the first four blocks of the task, for all groups.

Table 4.3. Mean Between-Block Variation in Performance for all Groups.

	Frontal Lesion Patients	Non-Frontal Lesion Patients	Controls	P-Value
EAT Errors (SE)	9.6 (1.5)	9.4 (1.5)	10.9 (1.4)	0.731
Awareness (SE)	18.2 (2.2)♣	12.8 (2.1)	9.1 (1.9)♣	**0.013**
Omissions (SE)	1.6 (0.4)♣	0.6 (0.3)	0.4 (0.3)♣	**0.040**

Note: SE = Standard Error.

Bonferroni Comparisons: ♣ Frontal Lesion Patients vs Controls ($p < 0.05$).

[4] Four was the minimum number of blocks completed by all participants.

4.3.4 ERP Results

4.3.4.1 Correct Response Negativity (CRN) and Error-Related Negativity (ERN) at Fz

For CRN/ERN amplitudes, a mixed repeated-measures ANOVA with between-subjects factor Group (3 levels: Frontal Lesion patients, Non-Frontal Lesion patients and Controls) and within-subjects factor Response Condition (2 levels: Correct Response and Error) revealed a main effect of Response Condition [$F(1, 32) = 24.249$, $p < 0.01$], and a significant interaction between factors [$(F(2, 32) = 3.326$, $p < 0.05$], with no main effect of Group [$F(2, 32) = 1.01$, $p > 0.05$]. Separate follow-up univariate ANOVAs revealed that ERN amplitude did not differ between groups [$F(2, 32) = 0.224$, $p > 0.05$]. CRN amplitude however, showed a group effect [$F(2, 32) = 4.113$, $p < 0.05$], in that frontal lesion patients showed significantly larger CRN amplitudes than non-frontal lesion patients ($p < 0.05$) and controls, where the difference between frontal lesion patients and controls approached significance ($p = 0.063$). Subsequent paired t-tests – performed separately for each group - revealed a significantly larger negative amplitude following errors than correct go responses among controls [$t = 6.742$, $df = 14$, $p < 0.01$] and non-frontal lesion patients [$t = 2.404$, $df = 9$, $p < 0.05$]. Among frontal lesion patients, however, amplitudes for these two responses conditions did not differ significantly [$t = 0.884$, $df = 9$, $p > 0.05$]. This demonstrates that controls and non-frontal lesion patients showed a small CRN following correct trials and a larger-amplitude ERN following

errors, while CRN and ERN amplitudes did not differ among frontal lesion patients.

For latency of these negativities, the ANOVA showed no main effect for Response Condition [$F(1, 32) = 1.173$; $p > 0.05$], Group [$F(2, 32) = 1.105$; $p > 0.05$] or interaction between factors [$F(2, 32) = 0.595$; $p > 0.05$], suggesting that ERN and CRN latencies did not differ from each other or between groups (mean CRN latency – Controls: 65.8ms, Frontals: 68.0ms, Non-Frontals: 62.9ms; mean ERN latency – Controls: 83.5ms, Frontals: 77.4ms, Non-Frontals: 60.8ms).

Figure 4.4 shows the grand-average ERP waveforms elicited by correct responses and aware errors at Fz, where ERPs were maximal. ERPs are shown separately for each group. Figure 4.5 below shows the scalp topographies of the ERN for all three groups, showing the clear negative peak at the fronto-central electrodes among controls and non-frontal lesion patients, which is significantly less well developed around the fronto-central sites.

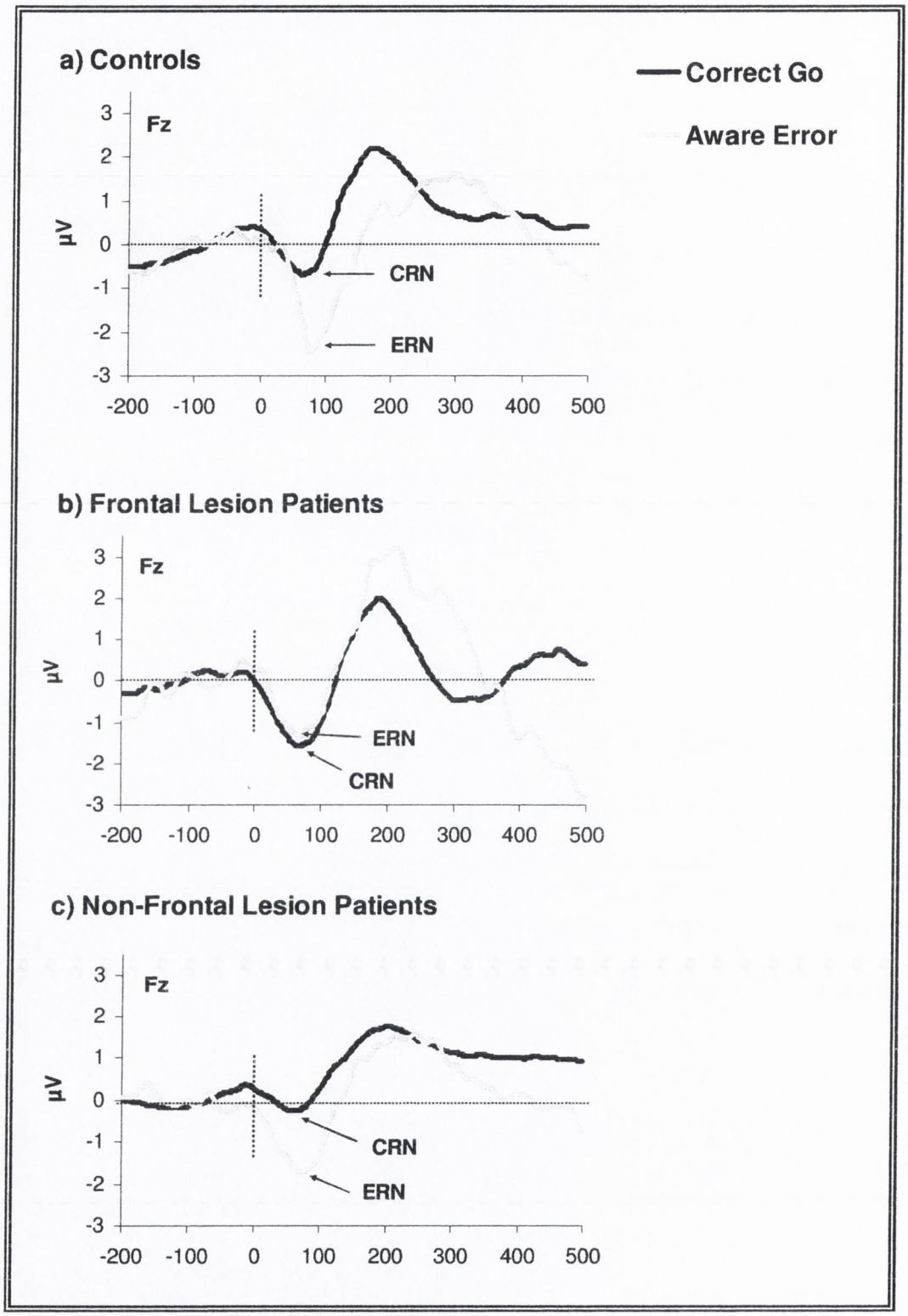


Figure 4.5. ERP Grand-averages at Fz for each Group.
a) Shows control participants' grand-averages for correct responses and aware errors, with a clearly differentiated ERN following error trials. CRN amplitudes were significantly smaller. b) Shows grand-averages for frontal lesion patients at Fz, where negative amplitudes following correct and error responses did not differ. c) Illustrates that grand-averages at Fz for non-frontal lesion patients also show a clearly differentiated ERN on error trials, and a much smaller CRN following correct go trials.

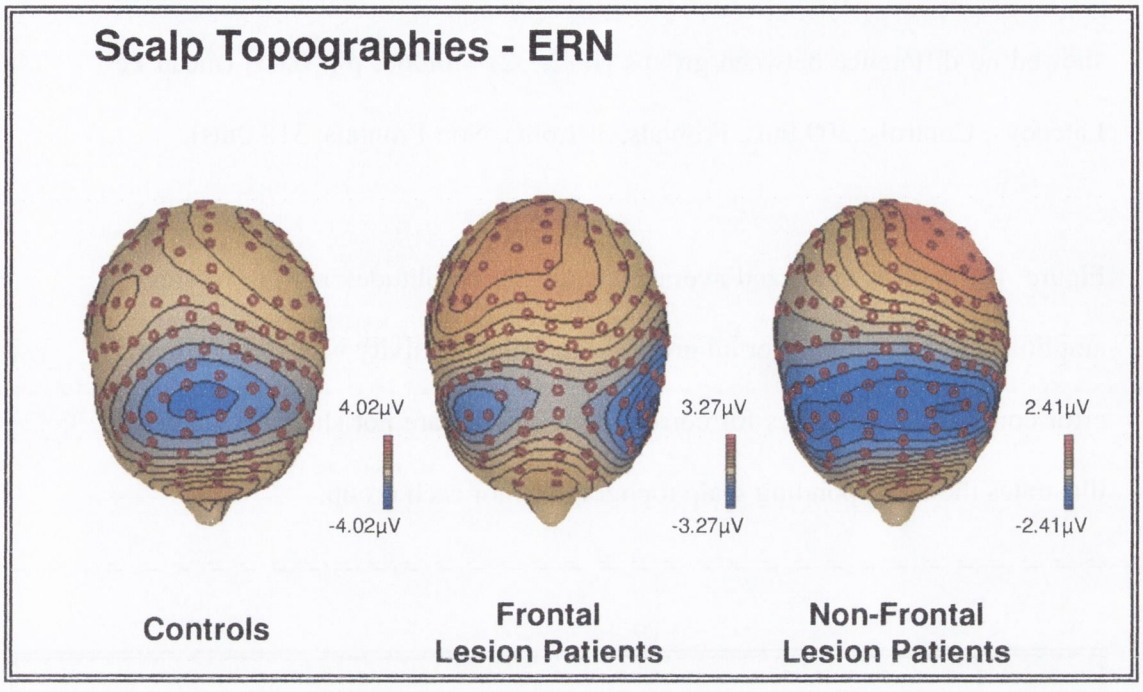


Figure 4.6. ERN Scalp Topographies for all Groups. The clear negative peak emerging around fronto-central electrodes (strongest at Fz) is missing for frontal lesion patients.

4.3.4.2 Error Positivity - Pe

For the amplitude of the Pe, the ANOVA showed a clear effect of Response Condition, [$F(1, 32) = 67.079$, $p < 0.01$], as well as an effect of Group [$F(2,32) = 5.879$, $p < 0.01$] and no Group by Response Condition interaction [$F(2, 32) = 0.672$, $p > 0.05$]. Bonferroni comparisons indicated that across all groups, positive amplitudes were larger following errors than correct responses ($p < 0.001$). However, following errors, non-frontal lesion patients showed significantly smaller Pe amplitudes than both controls and frontal lesion patients (both $p < 0.05$).

Latency of the Pe peak was compared using a univariate ANOVA, which showed no difference between groups [$F(2, 32) = 0.068$, $p > 0.05$] (mean Pe Latency – Controls: 309.0ms, Frontals: 301.6ms, Non-Frontals: 318.0ms).

Figure 4.6 depicts the grand-average of the Pe amplitudes at Cz (where Pe amplitude was maximal), for all groups. Since the positivity was specific to the error condition, amplitudes for correct go responses are not shown. Figure 4.7 illustrates the corresponding scalp topographies for each group.

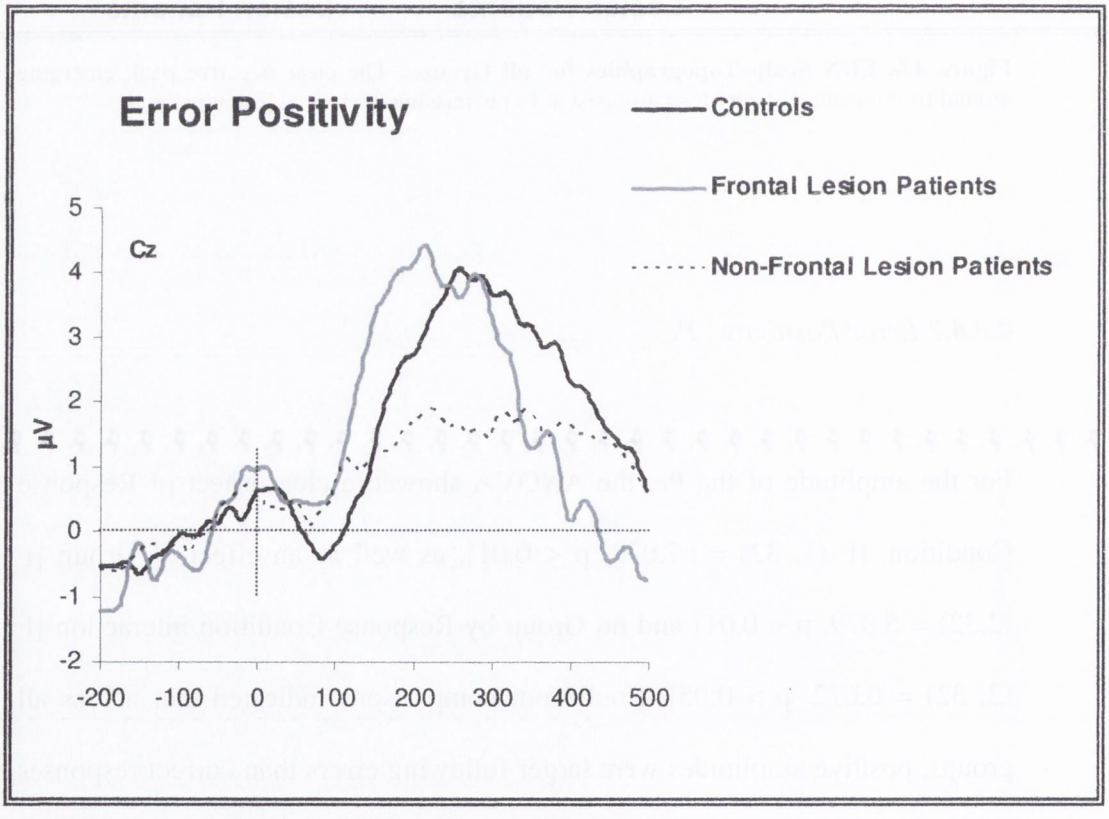


Figure 4.7 Error Positivity (Pe) at Cz for all Groups. Shows the Pe amplitudes recorded from Cz, as a function of group. Non-Frontal lesion patients show a significantly attenuated Pe peak.

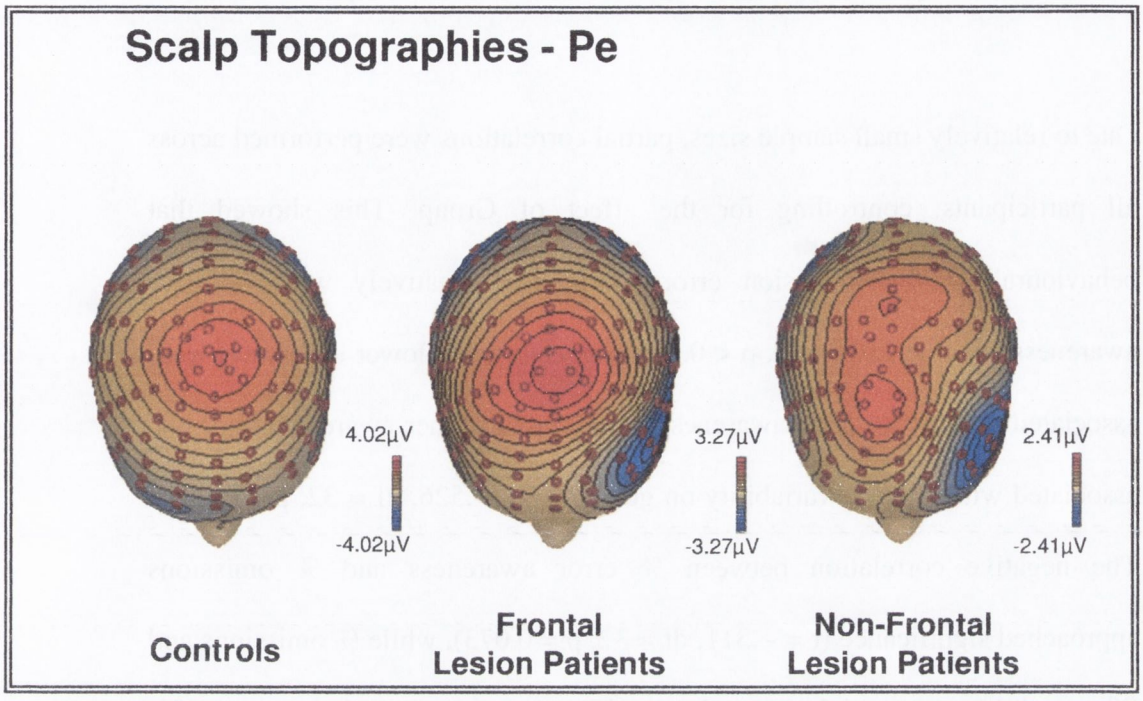


Figure 4.8 Pe Scalp Topographies. Shows the scalp topography of the Pe. While controls and frontal lesion patients show a clear positive component emerging over central electrodes, this peak is less well-defined in the non-frontal lesion group grand-average.

4.3.5 Relationship Between Time Since Lesion and ERP Components

Pearson correlation coefficients were computed to examine the relationship between patients' Time Since Lesion (TSL, measured in months) and error-related ERP components. TSL did not correlate significantly with either ERN amplitude or latency, nor Pe amplitude or latency (all $N = 20$, $p > 0.05$).

4.3.6 Relationship Between Task Performance and ERP Components

Due to relatively small sample sizes, partial correlations were performed across all participants, controlling for the effect of Group. This showed that behaviourally, % commission errors correlated negatively with % error awareness ($r = -.392$, $df = 32$, $p < 0.05$), suggesting that lower error rates were associated with better error awareness on the task. Higher awareness was also associated with less RT variability on go-trials ($r = -.526$, $df = 32$, $p < 0.001$). The negative correlation between % error awareness and % omissions approached significance ($r = -.311$, $df = 32$, $p = 0.073$), while % omissions and RT variability on go-trials showed a significant positive correlation ($r = .655$, $df = 32$, $p < 0.001$).

With regard to ERP components, no statistically significant relationships could be demonstrated, although a number of correlations approached significance: ERN amplitude correlated negatively with omission errors ($r = -.307$, $df = 32$, $p = 0.078$). ERN latency was negatively associated with RT variability on go-trials ($r = -.299$, $df = 32$, $p = 0.075$), which suggests that participants with variable go RTs also showed a delayed ERN peak. Lastly, Pe amplitude showed a positive relationship with error awareness, which also fell just short of statistical significance ($r = 0.310$, $df = 32$, $p = 0.075$), such that higher awareness levels on the task were associated with larger amplitudes of the Pe. The correlation matrix is displayed in Table 4.4 below.

Table 4.4 Coefficients for Partial Correlations Between ERPs and Task Performance

	% Errors	% Error Awareness	RT Variability	% Omissions	ERN Amplitude	ERN Latency	Pe Amplitude	Pe Latency
% Errors		**-.392***	.186	-.019	.037	-.105	-.143	-.104
(p-value)	------	**(0.022)**	(0.294)	(0.916)	(0.836)	(0.555)	(0.418)	(0.559)
% Error Awareness			**-.526****	**-.311**	.086	.106	**.310**	-.147
(p-value)		------	**(0.001)**	**(0.073)**	(0.627)	(0.551)	**(0.075)**	(0.408)
RT Variability				**.656****	.187	**-.299**	-.265	.134
(p-value)			------	**(0.000)**	(0.290)	**(0.085)**	(0.129)	(0.451)
% Omissions					**-.307**	-.204	-.143	-.077
(p-value)				------	**(0.078)**	(0.246)	(0.421)	(0.664)
ERN Amplitude						-.054	-.070	-.070
(p-value)					------	(0.760)	(0.693)	(0.695)
ERN Latency							.138	-.047
(p-value)						------	(0.435)	(0.794)
Pe Amplitude							-------	-.150
(p-value)								(0.398)
Pe Latency								
(p-value)								------

Note: * $p < 0.05$; ** $p < 0.01$, uncorrected for multiple comparisons. Coefficients are highlighted in bold where statistical significance was reached or approached.

4.3.7 Relationship Between ERP Components and Neuropsychological Performance

Partial correlations (controlling for the effect of group) were performed between all neuropsychological scores and the amplitude of the ERN and Pe. No significant correlations emerged (all $p > 0.05$).

4.3.8 Relationship with Other Awareness Measures

In order to establish whether the error awareness effects of the current study were specific to the EAT, participants were examined in terms of the self-awareness measures described in Chapter 3. Specifically, groups were compared on metacognitive awareness and awareness of errors during the Sustained Attention to Response Task (SART), using univariate ANOVAs. For metacognitive awareness, a group effect [$F(2, 37) = 6.347$, $p < 0.05$] followed by Bonferroni comparisons showed that frontal lesion patients significantly under-estimated their symptoms, compared to controls ($p < 0.01$). The difference between non-frontal lesion patients and controls came close to significance ($p = 0.051$), with the mean score suggesting that non-frontal lesion patients also under-estimated their difficulties, however not to the same degree as frontal lesion patients.

For error awareness during SART, the ANOVA also showed a group difference [$F(2, 37) = 4.323$, $p < 0.05$], and Bonferroni comparisons confirmed

that frontal lesion patients showed significantly lower awareness than controls ($p < 0.05$). Again, the difference between non-frontal lesion patients and controls approached significance ($p = 0.058$).

Mean values for metacognitive and SART error awareness are shown in Table 4.5 below. Metacognitive awareness is expressed in terms of z-scores, where negative values indicate under-estimation of symptoms and difficulties (see Section 3.3.5 in Chapter 3). SART error awareness is expressed as the percentage of errors reported as aware during SART (see Section 3.3.6.1 in Chapter 3).

Table 4.5. Metacognitive and SART Error Awareness For Frontal, Non-Frontal Lesion Patients and Controls.

	Frontal Lesion Patients	Non-Frontal Lesion Patients	Controls	P-Value
Metacognitive Awareness (Z-Score) (SD)	-0.52 (0.5)♣	-0.02 (0.6)	0.16 (0.4)♣	**0.004**
SART Error Awareness (%) (SD)	32.09 (30.9)♣	33.84 (24.7)	58.52 (24.4)♣	**0.021**

Note: ♣ Frontal Lesion Patients vs Controls ($p < 0.05$).

4.3.9 Error Awareness and Side of Lesion

The sample of the current study consists of both left and right focal lesion patients. Given that the effect of reduced error awareness during SART described in the previous chapter was specific to *right* frontal lesion patients, error awareness during the EAT was briefly examined as a function of lesion side. Inferential statistics were not computed due to small group sizes, however, descriptive statistics confirmed that both left and right non-frontal lesion patients showed lowest awareness during EAT, while both frontal lesion groups displayed near-normal awareness. Mean values and standard deviations are presented in Table 4.6.

Table 4.6. Mean Error Awareness during EAT for Left and Right-Sided Frontal and Non-Frontal Lesion Patients.

	LF Lesion	RF Lesion	LNF Lesion	RNF Lesion	Control
EAT Error Awareness (SD)	81.9 (8.5)	85.7 (11.2)	62.2 (16.5)	77.3 (10.8)	88.7 (8.8)

4.4 Discussion

This study sought to examine electrophysiological correlates of conscious error awareness in frontal and non-frontal focal lesion patients. Patients and matched control participants completed a go/no-go task, which allowed errors to be explicitly acknowledged by participants, such that an error awareness percentage could be calculated. Error-related ERP components could thus be extracted, and compared between groups.

Across all blocks of the Error Awareness Task (EAT), the percentage of commission errors was equal between groups, suggesting that all groups were able to perform the task to a comparable degree. Error rates are also comparable to previous studies which have used the EAT in this form, i.e. by emphasizing speed and accuracy equally (Hester et al., 2005; Shalgi, O'Connell, Deouell, & Robertson, 2007). In terms of awareness of these commission errors, non-frontal lesion patients performed most poorly. Additionally, non-frontal patients also showed more variable go-trial RTs. The only behavioural effect of frontal lesions on performance across all blocks was a significantly higher percentage of omission errors. Given the contrasting findings from the previous two chapters, additional analyses were performed, which compared participants' variation in performance between individual task blocks. Results suggest that frontal lesion patients' error awareness and % omission errors varied significantly more between blocks, compared to the relatively stable performance of controls.

ERP components were analysed across all blocks, separately for correct go-trial responses and aware errors of commission. Among controls, the error-related negativity (ERN) was observed as a fronto-central peak, approximately 85 ms after erroneous button press. A smaller negative peak of similar latency was observed following correct button presses, a component which has been termed the correct-related negativity (CRN; Vidal et al., 2003; Vidal et al., 2000). The second error-related component of interest, the error-positivity (Pe) was also observed among controls, peaking approximately 310ms after aware errors, at slightly more posterior central sites. These findings are in keeping with O'Connell et al. (2007), showing that the EAT can be used to examine error detection and awareness networks through error-related ERP components.

Group comparisons showed that frontal lesion patients failed to show an electrophysiological distinction between correct and error trials, as illustrated in Figure 4.5b. A diminished amplitude difference between errors and correct responses has been reported in previous studies of patients with frontal lobe lesions and other types of frontal systems dysfunction. Such a result can arise from either an attenuated ERN in these patients, or an increase in CRN amplitude, and studies differ with respect to the specific origin of the effect. The present results show a specific increase in CRN amplitude for frontal lesion patients, while ERN amplitudes remained equal between groups, causing the typical effect of a large error-related response to vanish. These findings specifically replicate those of Gehring & Knight (2000), whose patients with damage to the lateral prefrontal cortex (LPFC) showed precisely the same pattern. In contrast, the series of LPFC patients reported on by Ullsperger and

colleagues (Ullsperger & von Cramon, 2006; Ullsperger et al., 2002) showed a specific decrease in ERN amplitude. These authors suggest that the type of task used may have been a significant factor in determining the difference in ERP findings, in that Gehring and colleagues used a task which poses high working memory and task-set managing demand on participants, by presenting a cue prior to each trial. In the current study, the same claim can be made, in that the EAT required participants to process go/no-go stimuli, while also performing a dual task to indicate awareness of errors. Although the CRN was observed on compatible colour trials, which arguably involve relatively low response conflict, participants must still maintain a representation for three scenarios: press for congruent go-trials, don't press for incongruent trials, and additionally, follow with an awareness button press after errors. Thus, the increased CRN may reflect activity that indexes the resolution of response conflict, imposed by the preparation for three potential responses – go, no-go and press to indicate awareness. The LPFC has been shown to be involved in processes such as maintenance and updating of representations in for task preparation (e.g. Derrfuss, Brass, & von Cramon, 2004). It is conceivable then that the task used by Gehring & Knight, as well as the current one, made higher demands on these processes than the simple flanker task used by Ullsperger and colleagues, and that this accounts for the difference in results. A simple way to test whether task demands can account for the inconsistency between studies would be to examine the ERN and CRN under conditions of high and low response conflict, and to test for post-error interference effects (Ridderinkhof et al., 2002).

Error awareness was adversely affected by non-frontal lesions in this study. Additionally, non-frontal lesion patients had more variable go-trial RTs than controls, and also omitted more go-trial targets, although this difference was not significant. The effect of a reduced awareness score across all blocks was accompanied by a significantly attenuated error positivity (Pe) among non-frontal lesion patients, compared to controls and frontal lesion patients. Additionally, a positive relationship between Pe peak amplitudes and error awareness emerged, which approached statistical significance. These two findings lend strong support to the notion of the Pe as an electrophysiological marker of conscious error awareness (Belopolsky et al., 2008; Endrass et al., 2005; Endrass et al., 2007; Nieuwenhuis et al., 2001; O'Connell et al., 2007). The finding of an unaffected Pe peak among our frontal lesion patients stands in apparent contrast with a number of previous patient studies: Ullsperger & von Cramon (2006) and Ullsperger et al. (2002) have shown a reduced Pe in their LPFC patients, and similarly, the Pe was shown to be attenuated following bilateral medial prefrontal cortex (MFC) injury (Stemmer et al., 2004). However, in other groups of patients where frontal systems dysfunction is prominent, including Parkinson's Disease, Alzheimer's Disease and schizophrenia, a number of studies have also failed to show a significantly decreased Pe (Alain, McNeely, He, Christensen, & West, 2002; Bates, Liddle, Kiehl, & Ngan, 2004; Falkenstein, Willemssen, Hohnsbein, & Hielscher, 2005; Mathalon et al., 2003; Mathalon et al., 2002). Importantly, no patient study to date has measured error awareness explicitly. It is therefore conceivable that inconsistencies in Pe findings may have arisen because a combination of aware and unaware errors was used to elicit the Pe.

Given the more posterior, centro-parietal distribution of the Pe, it is not too surprising that patients with posterior lesions would present with an altered Pe morphology. Blakemore & Frith (2003) have summarized the evidence which implicates parietal cortices, including the precuneus, in action awareness, and the source localization study of O'Connell et al. (2007) also produced a model which pointed to the precuneus as a contributing neural source of the Pe. It is also noteworthy that the Pe shows similarities with the P3 (Davies, Segalowitz, Dywan, & Pailing, 2001; Falkenstein et al., 2000; Nieuwenhuis, Aston-Jones, & Cohen, 2005), a component thought to reflect subjective evaluation of motivationally significant stimuli, for which the temporoparietal junction is important (e.g. Knight & Scabini, 1998). For non-frontal lesion patients in the present study, temporal and/or parietal networks are likely to have been disrupted, although caution is warranted since brain scans were acquired for clinical purposes only, and refined anatomical analyses were not provided.

Since only aware errors were analysed in this study, the findings suggest that non-frontal lesion patients processed aware errors *differently* than controls and frontal lesion patients. How these processes were altered is difficult to deduce from the present study, and may be best examined during task performance, using functional neuroimaging. What remains surprising, however, is that findings from the previous two chapters clearly implicated frontal systems for online awareness of errors. The frontal lesion patients selected to participate in the current study showed decreased metacognitive awareness and also lower awareness of errors during the Sustained Attention to Response Task (SART), as Table 4.5 shows. Additionally, when lesion side was considered, results

confirmed that even those right frontal lesion patients who had shown poor SART error awareness exhibited no impairment in awareness of EAT errors (see Table 4.6). It is possible that characteristics of the EAT – relatively bright colours, multiple task demands, etc - may have served as a form of exogenous alerting mechanism, which benefits right frontal lesion patients when errors occur. Indeed, Shalgi et al. (2007) have shown that encouraging a more monotonous response mode during the EAT, and thereby reducing the effectiveness of this exogenous alerting mechanism, *decreases* error awareness, presumably by placing higher demands on frontal systems to maintain top-down control over alertness levels and keeping awareness optimal and stable over time. Thus, right frontal lesion patients would be predicted to show lower awareness rates if the task was less a more monotonous one, as was shown in the previous chapter.

Correlational analyses failed to show a significant association between patients' Time Since Lesion (TSL) and ERP components. As previously suggested in Chapter 3, this may be partially explained by the fact that patients took part in the study at post-acute stages *only*, with mean TSL values of 61 and 58 months for each patient group. Separate analyses showed that ERP components were associated with aspects of task performance, with statistical significance falling just short of the $p = 0.05$-level. The amplitude value of the ERN correlated negatively with the percentage of omission errors, suggesting that higher omission rates were associated with an ERN of smaller amplitude. If the ERN can indeed be considered an electrophysiological correlate of performance control, then this relationship suggests that those participants who

had smaller ERN responses also performed less efficiently by omitting go-trial targets. Significant relationships between ERP components and neuropsychological functions were markedly absent. A possible explanation for this absence may be that the EAT does not elicit ERP components of the same magnitude as for example flanker tasks or response choice tasks which lead to errors. Thus, the relatively small voltage amplitudes observed in the present study may not give rise to the necessary range of values to examine significant relationships between neuropsychological and electrophysiological values.

The behavioural results of the present study suggest that among frontal lesion patients, error awareness fluctuated between blocks. Variability of performance - often but not always measured in RT tasks - has often been related to the efficiency of frontal systems functioning (e.g. Murphy, West, Armilio, Craik, & Stuss, 2007; Stuss, Murphy, Binns, & Alexander, 2003), and is closely related to the ability to sustain processing resources over extended periods of time. Therefore, a more detailed analysis of the factors preceding these fluctuations in awareness may be of benefit. In the present study, however, electrophysiological data could only be investigated in grand-averaged waveforms, due to the requirement of multiple error-trials for analysis of error-related ERP components. Therefore, ERP correlates in the current study could only be examined as averages across all blocks completed, since individual blocks of EAT did not give rise to sufficient amounts of errors for analysis. Future studies investigating the role of frontal systems for error awareness

should perhaps focus on the role of variability over time, and the mechanisms which cause fluctuation of awareness.

As in the previous study, the reported effects did not in all cases show a clear dissociation between patient groups. While the ERP findings showed statistically significant (or close to significant) differences between one patient group *and* controls, this was not the case for the behavioural results, where non-frontal lesion patients, for example, differed from controls but not from frontal lesion patients. Future studies must examine the difference between patient groups carefully, perhaps with specific reference to variation over time, as discussed above.

In conclusion, the present study has shown that across an entire experimental session, frontal lesion patients showed relatively intact error awareness, which stands in marked contrast to the findings of the previous chapter. A possible interpretation may be that online awareness can be further fractionated, and may vary with individual task characteristics, depending on whether or not the task itself exogenously increases participants' level of arousal. The following chapter will discuss this issue further by drawing together the findings from all experimental chapters of this thesis, and discussing them in terms of the theoretical models of self-awareness.

Chapter 5 : General Discussion

5.1 Summary and Evaluation of Studies

The studies described in this dissertation aimed to examine self-awareness from a neuropsychological, neuroanatomical and electrophysiological perspective. Study 1 began by focusing on the neuropsychological correlates of self-awareness among neurologically healthy young adults. Studies of this type are extremely rare, with predominant emphasis in the literature on self-awareness deficits among clinical population groups. As a result, there is little evidence regarding the validity of the measures used to assess self-awareness for non-clinical populations, and even less is known about how different levels of self-awareness may map onto neuropsychological profiles in the normal population. In study 1, two types of self-awareness deficit were measured that can be observed among individuals with brain injury (Toglia & Kirk, 2000) – metacognitive awareness and online awareness. Three sub-groups of participants were identified: those who under-estimated their cognitive symptoms on a number of scales; those who accurately appraised their symptoms; and those who perceived their symptom levels as disproportionately high without confirmation from their informant that this was indeed the case. The "under-estimator" group (i.e. those deemed to have poor metacognitive awareness) emerged as showing considerably poor sustained attention abilities. This supports previous findings that self-awareness and sustained attention are closely linked, among clinical patient groups (McAvinue et al., 2005;

O'Keeffe, Dockree et al., 2007b; O'Keeffe, Murray et al., 2007). Prospective memory was also related to online error awareness, supporting a proposal that awareness relies crucially on the efficiency frontal control systems.

From a relatively large battery of neuropsychological tasks, this sustained attention score was the only neuropsychological measure which differentiated between the groups. This may at first seem somewhat unusual, since all measures were chosen because they reflected abilities which had previously been associated with impaired self-awareness in clinical groups. However, it must be borne in mind that these individual neuropsychological tasks are designed to detect specific impairment in cognitive function, most frequently in clinical settings. Considering the mean scores obtained from the three awareness groups for neurocognitive domains such as 'memory', it is clear that no such clinical impairment existed among these participants. With respect to 'executive function', the scores on verbal fluency (FAS) fell within the norms specified by Ruff, Light, Parker, & Levin (1996) for young adults of similar educational background. Similarly, the error scores observed on the go/no-go task did not deviate from those provided in other studies using the same task (Hester et al., 2005), in fact participants in the current study performed slightly better. Equally, the primary measure of awareness in this study was a discrepancy score on a clinical scale. Future studies may need to make use of scales which can detect more subtle individual differences in cognitive functioning, and focus on awareness of those, among healthy young adults.

Interestingly, the scores on the Revised Strategy Application Task (R-SAT; Levine et al., 2000) across all three awareness groups were as low as those

previously reported for TBI patients, for whom the task was initially developed (Dockree, O'Keeffe et al., 2006; Levine et al., 2000; O'Keeffe, Dockree et al., 2007a). Bearing in mind that the R-SAT is a recently developed task and large-scale normative studies are as yet not available, one obvious difference between these studies and the current one is that participants in the study of Chapter 2 were younger than those individuals who would usually be recruited to match a patient group. The development of the executive functions continues until well beyond late adolescence (Casey, Giedd, & Thomas, 2000), paralleling continued frontal lobe maturation until individuals reach their late 20s (Sowell, Thompson, Holmes, Jernigan, & Toga, 1999). Therefore, it is conceivable that the low R-SAT score in current sample of healthy adults in their early to mid – 20s reflects may have shown low scores on the R-SAT as a result of less well-matured skills in the domain of controlled strategy application. Developmental changes in neural matter have been shown to differ between individual regions of the frontal cortex (Markham, Morris, & Juraska, 2007), which may account for the fact that other executive functions, such as verbal fluency and go/no-go errors were unimpaired in these participants. As highlighted previously, the term 'executive functions' incorporates a range of skills, and should not be considered a one-dimensional ability (Varney & Stewart, 2004). Perhaps a more detailed investigation of executive abilities and their relation to self-awareness among non-neurological participants is warranted for the future, given the prevalence of executive dysfunction as a correlate of impaired self-awareness in clinical studies.

The results of Study 1 also highlighted the importance of emotional function for self-awareness, in that online awareness of errors correlated negatively with

anxiety, among those who had poor metacognitive awareness. The question of causation of this relationship was discussed in Chapter 2. A remaining limitation of the study is the small sample size for individual awareness groups, particularly for the "under-estimators". It is therefore questionable to what extent the present findings may generalize to other healthy young adult populations, and replication with a larger sample size is warranted, to allow for an analysis of predictors of awareness levels. Study 1 was limited by practicality, in that it represented an exploratory attempt to capture fluctuating awareness among young adults, where awareness itself was established by comparing 'self' - and 'other' ratings on questionnaires. A scenario where individuals were screened for metacognitive awareness prior to neuropsychological assessment would be ideal for a large-scale examination of the cognitive and emotional profile of poor self-awareness among healthy young adults.

Although the findings of reduced sustained attention capacity implicate frontal control systems for self-awareness, this link is an indirect one, and was explored further in Study 2. This study investigated the neuroanatomical underpinnings of self-awareness, by comparing the effects of left and right frontal lobe injury, as well as left and right non-frontal neural injury, on three levels of self-awareness: metacognitive, online emergent and online anticipatory awareness (Crosson et al., 1989; Toglia & Kirk, 2000). Given the frequency with which the frontal lobes, and specifically right prefrontal cortices, have been implicated in self-awareness (as reviewed in Section 1.5 of Chapter 1), it was hypothesized that right frontal lobe lesion patients would score relatively poorly on the self-awareness measures used in this study.

Importantly, to the author's knowledge, no study to date has systematically compared self-awareness in large patient groups with injury in four distinct neuroanatomical regions.

Consistent with frontal lobe models of self-awareness (e.g. Stuss & Benson, 1986; Stuss, Picton et al., 2001), both left and right frontal lesion groups showed poor metacognitive awareness, as assessed by discrepancy between 'self' and 'other' ratings on a number of questionnaires. Additionally, these two frontal lesion groups also rated their level of behavioural change since injury as less severe than their significant others. This was measured on the FrSBe scale only, and therefore the effect only accounts for patients' perception of change in symptoms of frontal systems damage, i.e. apathy, disinhibition and executive function. It is possible, however, that a patient's perception of change may differ for different domains, for example concrete everyday behavioural functions, emotional function, etc. The modular nature of deficit awareness has been emphasized by a number of studies (Prigatano, 1996a; Spinazzola et al., 2008), and current research is investigating the possible differential neuroanatomical underpinnings of such 'modular unawareness'. In the present study, the perception of patients' 'self' was only examined on the FrSBe, since other scales such as the Patient Competency Rating Scale (PCRS) and Cognitive Failures Questionnaire (CFQ) do not provide separate sub-scales for symptoms 'At Present' and 'Before Injury'.

Additionally to the self-awareness measures pertaining to questionnaire data, online awareness of errors on the Sustained Attention to Response Task (SART) (or online emergent awareness) was compared among the four patient

groups and healthy control participants. Right frontal lesion patients showed a considerable impairment in the ability to monitor their erroneous responses, a deficit which was accompanied by a reduced skin conductance response (SCR). This reduced response was specific to errors which right frontal patients *had* indicated as occurring under awareness, suggesting that autonomic reactivity to incorrect responses was attenuated. The process of 'labelling' our responses autonomically to guide future behaviour has been described by Damasio's (1994) 'somatic marker' hypothesis, which implicates frontal cortices in generating these autonomic signals. When the top-down control of these 'somatic markers' is disrupted, individuals cannot make fine-tuned performance adjustments, since erroneous responses are never appraised as an unpleasant occurrence to be avoided. The tendency for unaware patients to show little concern and inappropriate emotional reactions to their diagnosis has been noted throughout the literature (e.g. Orfei, Robinson, Bria et al., 2007), and studies examining the relationship between this phenomenon and unawareness itself are lacking. The results from study 2 suggest that the attenuated autonomic response to errors may have contributed to the overall deficit in monitoring for errors among right frontal lesion patients.

An additional awareness type that was compared between lesion groups and healthy controls was 'anticipatory' awareness, which was measured as the ability to predict performance on a range of simple cognitive tasks. A complex pattern of results emerged: left frontal lesion patients had a tendency to over-estimate how well they would perform, but adjusted their estimate downward accordingly once they had performed the task. As a group, left frontal lesion patients made the most adjustment to their initial estimate. Controls made the

least adjustments out of all groups, which is unsurprising since they also provided the most conservative estimates of their performance (both before and after task completion). Right frontal lesion patients made small adjustments following task completion, but also provided slightly conservative performance estimates prior to task begin. Thus, although right frontal lesion patients cannot be considered to have shown impaired anticipatory awareness, they nonetheless showed relatively little change in their estimate once they had completed the task. The finding that left frontal lesion patients were adequately adjusting their estimate supports the notion that they were able to react appropriately to errors and strategically respond to them, whereas SART results suggest that right frontal lobe lesion patients could not. Further examination of anticipatory awareness among frontal lesion patients, however, is warranted to determine whether different types of cognitive tasks may influence performance estimates prior to and following task completion.

Further results from Study 2 showed a relationship between metacognitive awareness and sustained attention capacity, confirming the findings of Study 1. Additionally, metacognitive awareness correlated with FrSBe (Other) scores, and anticipatory awareness, which had not been examined in Study 1, was associated with verbal fluency measures and sustained attention score. Online emergent awareness was not associated with any measure of frontal systems function, which stands in contrast with the correlational results from Study 1. Interestingly, no relationship emerged between the time lapse since injury among patients, and any of the awareness measures. Given that impaired self-awareness is frequently observed in acute stages of injury, and considered to resolve gradually during recovery stages (Prigatano, 2003), this is a somewhat

surprising result, which highlights the need for systematic studies of the emergence of awareness following different types of neural injury.

Based on the findings from Study 2, regarding the importance of left and right frontal cortices for differing types of self-awareness, Study 3 aimed to investigate the impact of frontal and non-frontal cortical lesions on a number of electrophysiological markers associated with the processing of response errors during cognitive tasks. The specific event-related potentials (ERPs) examined here were the error-related negativity (ERN, also known as Ne), shown to accompany erroneous responses, the correct-related negativity (CRN), sometimes observed following correct responses, and the error positivity (Pe), which appears to emerge only if an error occurs under awareness. These ERPs can reliably be extracted from the ongoing EEG recording of participants performing the Error Awareness Task (EAT; Hester et al., 2005; O'Connell et al., 2007).

The behavioural results of Study 3 showed that non-frontal lesion patients exhibited lowest awareness overall during this task. The electrophysiological findings matched the behavioural result, by showing that the centro-parietal Pe was significantly attenuated among non-frontal lesion patients. Additionally, frontal lesion patients failed to show the typically observed ERP distinction between correct and erroneous responses, which corroborates those results of Gehring & Knight (2000), as discussed in Chapter 4.

In terms of overall task performance, the only significant effect of frontal lesions appeared to be a higher rate of omission errors, compared to controls.

Further analysis showed that fluctuations in error awareness between individual task blocks were significantly larger among frontal lesion patients than controls. As already discussed in Chapter 4, this suggests that a more detailed electrophysiological analysis of awareness fluctuation may be warranted, to capture subtle characteristics which the current analysis may have missed. West & Travers (2008) have recently described an additional component that appeared specifically related to errors – a frontal slow wave between 200ms and 2000ms after the erroneous response – which may be amenable to trial-by-trial analyses. This component has not previously been described, and subsequently, its precise relationship to erroneous responding and other aspects of task performance remains to be investigated. Nonetheless it may illuminate the ongoing debate regarding the relevance of the ERN and CRN following errors and correct responses, respectively.

Considering the neuropsychological characteristics of the patients recruited for Study 3, it is noteworthy that non-frontal lesion patients showed lower scores than controls across the executive function measures, such as Self-Ordered Pointing Task (SOPT) and verbal fluency. It is therefore conceivable that the non-frontal lesion patients who participated in Study 3 suffered damage to components of a network which innervates frontal regions. Such disruption of frontal networks can lead to executive dysfunctions similar to those observed among frontal lesion patients (e.g. Goldberg & Bilder, 1987; Lezak et al., 2004). This possibility could only directly be ascertained using more sophisticated imaging techniques, for example Diffusion Tensor Imaging (DTI), with the patients in the present study. In lieu of such measures, however, neuropsychological results ascertained that non-frontal lesion patients

only showed lowered scores on *some* measures of frontal systems efficiency, while others, such as sustained attention, was unimpaired compared to frontal lesion patients. Further analyses also showed that other aspects of self-awareness (metacognitive and online awareness of SART errors) were unimpaired, suggesting that frontal systems were functioning relatively adequately in this non-frontal lesion group.

A caveat of both patient studies presented in this dissertation is that the effects of focal lesions were considered in isolation of any additional factors which may influence performance, such as functional re-organization, compensation, or indeed inflammation of areas remote from the lesion site (Block, Dihne, & Loos, 2005; Fellows et al., 2005). These issues constitute the pitfalls of any study which employs the lesion method, and their impact can only be partially lessened by comparing multiple groups of lesion patients, who should in theory be affected by these factors to comparable degrees (Fellows et al., 2005).

5.2 Integration with Existing Frameworks

In terms of existing theoretical models of self-awareness, the findings of Study 1 and 2 support the view of Stuss and colleagues (Stuss, 1991; Stuss & Benson, 1986; Stuss, Picton et al., 2001), who propose that impaired self-awareness is primarily a deficit in self-monitoring, arising directly from damage to the frontal lobes. Other authors have also suggested that a deficit in monitoring may account for unawareness syndromes, and have attempted to expand this framework to account for unawareness seen in patients with predominantly posterior damage and right hemisphere dysfunction, or indeed neurodegenerative disease (e.g. Agnew & Morris, 1998; Heilman, 1991; Marcel et al., 2004; Venneri & Shanks, 2004). Neuroimaging findings have previously shown that right frontal cortex is highly active when conflict arises between an intended and executed action (Fink et al., 1999), and the results of Study 2 demonstrate the necessity of this region monitoring action slips over relatively short periods of time.

In order to integrate the findings from Study 3, it is perhaps useful to consider in more detail the issue of the 'object' of awareness (e.g. Markova & Berrios, 2001). 'Objects' of awareness in Study 3 were go/no-go errors during a task which used colourful stimuli, at a relatively rapid pace. As discussed in Chapter 4, this task has previously been shown to elicit higher rates of unaware errors when a more monotonous response set is encouraged (Shalgi et al., 2007). Such monotony leads to a decrease in exogenous stimulation for participants, and in terms of a model of vigilant attention outlined by

Robertson & Garavan (2004), increases the demand on frontal control systems to keep processing resources at adequate levels to support functioning. In the current version of the task (Study 3), such monotony was not encouraged; rather, participants responded as quickly and accurately as they could. This rapid response mode, along with the stimuli themselves may have provided enough exogenous support to lessen the demand made on frontal control systems to keep participants alert and responding with efficiency. The effect of non-frontal lesions on error awareness can then be considered to corroborate findings which show that posterior cortical regions, including parietal areas, are part of a larger-scale network which serves to generate a sense of agency during movement (Blakemore & Frith, 2003). The specific roles and relative contributions of sensory feed-forward and feedback mechanisms in this network continue to be investigated, and were not a focus of the current dissertation.

The current findings also support those models which posit that self-awareness can be impaired in terms of several functional types (Crosson et al., 1989; Toglia & Kirk, 2000). Additionally, it may be possible that individual types of self-awareness may be particularly vulnerable to neural insult. For example, while metacognitive/intellectual awareness was impaired in both frontal lesion groups and also among adults with poor sustained attention function, left frontal lesions were associated with a specific deficit in anticipatory awareness. As discussed by Toglia & Kirk (2000), anticipatory awareness is most likely a complex function, drawing on a range of aspects, including beliefs and knowledge about the task, motivation, understanding of what is being required

("Estimate how well you will perform."). Systematic studies examining the relative importance of these factors are as yet lacking, and are required before the putative involvement of left frontal cortices can be evaluated fully.

What can be shown, based on the current results, however, is that the strict functional hierarchy of self-awareness deficits after brain injury, as proposed by Crosson et al. (1989) in the Pyramid Model, is questionable: Crosson's model viewed anticipatory awareness as the highest level of self-awareness, which could only be achieved if intellectual and online emergent awareness were intact. Similar to the findings of Abreu et al. (2001), the results presented here suggest that this may not necessarily be the case; despite impaired metacognitive awareness deficit, left frontal lesion patients showed intact emergent awareness. Thus, models which view self-awareness types as interacting in a dynamic and fully flexible manner, such as the Toglia & Kirk's (2000) Dynamic Comprehensive Interactional Model (DCIM), may capture a wider range of self-awareness impairments found in clinical populations.

5.3 Future Directions

In Study 1, one group of young adults emerged who showed remarkably consistent "over-estimation" of cognitive symptoms. This group, as previously mentioned in Chapter 2, could also be considered to be *unaware* of their cognitive functioning, although this kind of unawareness is more likely to be of complex psychological than neurological origin. Many authors have emphasized the interplay between neurological and psychological factors in determining self-awareness (e.g. Kortte, Wegener, & Chwalisz, 2003; Weinstein & Kahn, 1955), and undoubtedly, psychological denial of impairment constitutes a powerful coping mechanism, especially following traumatic injury or during stressful hospitalization periods (e.g. Bortz, Prigatano, Blum, & Fisher, 1995). Thus, in order for the current findings to be fully applicable to rehabilitation programmes, which are based on biopsychosocial models of illness and recovery, psychosocial aspects must be taken into account (Palmer & Wegener, 2003). As outlined in Chapter 1, the research presented here focused on neuroanatomical, neurocognitive and electrophysiological characteristics only, with specific reference to awareness of a *deficit* in cognitive function. Since the "over-estimators" in study 1 did not show such a deficit (as objectively rated through input from a significant other), further correlates of this type of 'unawareness' of functioning were not examined. Therefore, a useful extension of the current body of work would be to examine in detail why participants over-estimate the frequency of cognitive symptoms, as in the "over-estimator" group of Study 1. Additionally, as discussed in Section 2.4, future studies should explore the relationship between

those processes involved in error monitoring tasks and prospective memory tasks. Study 1 showed that both tasks may involve similar mechanisms, a hypothesis which merits further investigation, for example through the of fMRI techniques.

With respect to the two patient studies reported in this dissertation (Study 2 and 3), a similar direction could be explored, in that it would be illuminating to attempt to separate psychological from neurological factors in impaired awareness. Additionally, it would be helpful to dedicate further studies to the examination of *other* types of self-awareness than the ones described in this dissertation, such as explicit and implicit awareness (Ownsworth et al., 2006). Methodologically, the use of different approaches would be helpful here. O'Callaghan, Powell, & Oyebode (2006), for example, applied a more phenomenological approach, which focused on charting the subjective experience of gaining awareness in TBI patients, documenting the interplay between structured rehabilitation and patients' recovery experience outside the clinical environment.

For future studies of electrophysiological aspects of error detection and awareness, an examination of tonic measures of cognitive processing may be useful. O'Connell et al (2007), for example, showed that a significant relationship existed between tonic measures of cortical arousal – in the form of slow/fast wave ratios in the EEG spectrum – and awareness of errors. Electrophysiological analyses of this type may increase our understanding of the necessary 'setting conditions' in which accurate or erroneous responding

occurs, and to what extent these conditions are affected by acquired brain injury.

Finally, the patient studies reported herein were limited by practicality, in that the number of patients available for participation limited the sample sizes in each study. Since the primary goal was to systematically compare the effects of lesions which have previously been shown to impair awareness, series of case studies were not conducted. By necessity, this means that very detailed information, such as unique structure-function relationships for individual patients, influence of functional re-organization, etc., could not be included in the analyses. Additionally, individual patients' brain scans were clinical in nature, and could therefore not be standardised to allow analysis in terms of lesion size or volume. In all patient cases, consultants confirmed that neuroanatomical damage was predominantly in (right / left) frontal or non-frontal regions. This, however, does not exclude the possibility of other networks or even regions being affected, especially in cases where neuroimaging records could not be obtained. Future studies of this type should make use of techniques such as voxel- or stereology-based lesion-symptom mapping (Bates et al., 2003; Kalkan et al., 2007), which are currently being optimised in order to improve precision in relating brain structure to mind (Rorden, Karnath, & Bonilha, 2007).

5.4 Concluding Remarks

The studies presented in this dissertation aimed to extend previous research on neuropsychological, neuroanatomical and electrophysiological correlates of self-awareness, by considering awareness among non-neurological participants, directly comparing multiple forms of impaired awareness among large groups of focal lesion patients, and examining error-related ERPs in focal lesion patients and controls. The results suggested an important role for left and right frontal cortices to self-awareness, although the somewhat contrasting results in Study 3 should be considered a reminder that many open questions remain in this field. More systematic quantitative and qualitative reports are required, if we are to fully appreciate the complex nature of self-awareness and its disturbances.

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Appendix

Ethical Approval

Letters of Information and Consent

Patient Demographic Data

HAD Scale

MET Scale

CFQ

CFQ (For Others)

PCRS

PCRS (For Others)

SOPT Stimuli

Dr Kevin Tierney
Department of Psychology Ethics Committee
Trinity College Dublin
Dublin 2

Ms Doreen Hoerold
Postgraduate Researcher
Department of Psychology
& Institute of Neuroscience
Trinity College Dublin
Dublin 2

08 February 2005

Dear Dr Tierney,

RE: An investigation of sustained attention & awareness processes in focal frontal lesion patients.

Please find attached three copies of my application for ethics approval for the above-named research study.

As explained in more detail on the application form, none of the tests to be administered to this participant group involves invasive, harmful or clinical techniques. In terms of the proposed methodology, the sessions will include a standard battery of neuropsychological assessments, and a second session of computerised attentional tasks while monitoring participants' electroencephalographic activity. These tests and procedures have been frequently used in this department under supervision of Professor Ian Robertson, and have been approved by the committee in the past.

Furthermore, please note that ethical approval from the relevant medical authority – in this case Beaumont Hospital, with Dr Niall Pender as principal investigator – has already been obtained.

Should you have any further questions, please do not hesitate to contact either myself or Professor Robertson (ian.robertson@tcd.ie).

Sincerely,

D. Hoerold

Doreen Hoerold

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Department of Psychology
Ethics Committee

19/04/2005

Dear Doreen Hoerold.

The Department of Psychology Ethics Committee met recently to consider your application entitled
An investigation of sustained attention and awareness processes of frontal lesion patients.

I am pleased to inform you that the Committee has approved your application, subject to you making the following changes.

— indicate how data will be stored.
— approval is subject to approval of Hospital Ethics committee

Yours sincerely,

Kevin Tierney
Chairperson,
Department of Psychology Ethics Committee

IR

Letter of Consent:

For the attention of Research Participants

An investigation of attention and awareness in patients following focal brain injuries.

What is the project?

We would like to invite you to participate in a study which is looking at how the brain attends to information in the world.

Following injuries to the brain patients often experience difficulties concentrating and attending to details in the world around them. This can lead to difficulties with conversations, lapses of memory and day-today mistakes. Some patients also experience frequent tiredness which might be related to problems with attention.

These phenomena have been widely investigated in patients suffering from traumatic, widespread brain damage, while less is known about such effects in patients whose brain damage is more localised. We would like to learn more about attention processes in specific brain regions and how we might be able to help patients.

You have been chosen as a potential participant from the clinical records of the Department of Psychology, Beaumont Hospital, Dublin. Alternatively, you may have been chosen as a healthy control participant for comparative purposes.

Our study will involve two parts. The first involves some simple pencil and paper tests of thinking which you should not find difficult or distressing. The second part would involve completing some simple computer tasks while we measure electrical changes in your brain using an Electroencephalogram (EEG). This is a harmless tool which is used in Hospitals and is not unpleasant or invasive in any way. Rather, it involves placing electrodes on your scalp to measure brain activity during the computer tasks.

We have described the tasks in more detail below for your interest.

What exactly are the tasks?

A number of tasks have been developed to measure aspects of thinking such as attention, memory and planning ability. Some of the tasks are presented on a computer screen and others will be undertaken with pen and paper. The study involves two sessions:

(1) The first session will last a maximum of 2.5 hours and you will be given a series of pen and paper based tasks and computerized tasks which help us to understand memory, attention, and planning performance.

(2) The second session would consist of a further 2 hours with computer tests. During these tasks we will measure electrical activity from the brain by using an EEG. The EEG measures your brain's electrical activity by simple recorders called electrodes placed on your head. This is not unpleasant or distressing in any way. We will also place electrodes on your fingers to measure the electrical activity of your skin while you do the tasks. These procedures are harmless, do not cause any pain and are often used in Hospitals.

What are my rights if I join the study?

Participation in the study is entirely voluntary and if you agree to participate you have the following rights:

1. The information from this study will be kept strictly confidential and will not be made available to any other people.

2. We will aim to publish our results in scientific journals but any information we have will be completely anonymous and presented as a group.

3. As participation is completely voluntary, you are free to withdraw from the study at any time without it affecting present or future care by Beaumont Hospital.

3. Under the Freedom of Information Act you can have access to any information we store about you, if requested.

☐ I (the undersigned) consent to participate in the first part of this study. I understand that the first session involves only a neuropsychological assessment.

☐ I agree to be contacted in the future regarding my participation in the second part of the study.

Full Name: _____

Signed _____

Date _____

For further questions, please contact: Doreen Hoerold
Postgraduate Researcher
Department of Psychology & Institute of Neuroscience
Trinity College Dublin
Tel: 01 896 8405
Email: hoeroldd@tcd.ie

Letter of Consent

to obtain brain imaging data from Beaumont Hospital to complete the following research project:

" An investigation of attention and awareness in patients following focal brain injuries."

I, _____, hereby agree that my brain imaging data, as acquired at Beaumont Hospital, Dublin, may be used for research purposes by Ms Doreen Hoerold & Dr Niall Pender. Subsequently, I agree that those data may be further analysed and results be published in summary form in scientific journals in the future.

I understand that my agreement is voluntary, and does not affect my treatment at Beaumont Hospital in any way.

Signature: _____

Date : _____

Letter of Consent:

For the attention of Research Participants

An investigation of attention and awareness in patients following focal brain injuries.

What is the project?

We would like to invite you to participate in a study which is looking at how the brain attends to information in the world.

Following injuries to the brain patients often experience difficulties concentrating and attending to details in the world around them. This can lead to difficulties with conversations, lapses of memory and day-today mistakes. Some patients also experience frequent tiredness which might be related to problems with attention.

You have been chosen as a potential participant from the clinical records of the Department of Psychology, Beaumont Hospital, Dublin. Alternatively, you may have been chosen as a healthy control participant for comparative purposes.

This experiment involves completing a simple computer task while we measure electrical changes in your brain using an Electroencephalogram (EEG). This is a harmless tool which is used in Hospitals and is not unpleasant or invasive in any way. Rather, it involves placing electrodes on your scalp to measure brain activity during the computer tasks.

What are my rights if I join the study?

Participation in the study is entirely voluntary and if you agree to participate you have the following rights:

1. The information from this study will be kept strictly confidential and will not be made available to any other people.

2. We will aim to publish our results in scientific journals but any information we have will be completely anonymous and presented as a group.

3. As participation is completely voluntary, you are free to withdraw from the study at any time without it affecting present or future care by Beaumont Hospital.

4. Under the Freedom of Information Act you can have access to any information we store about you, if requested.

☐ I (the undersigned) agree to participate in the EEG (electroencephalogram) study conducted at Trinity College Institute of Neuroscience, TCD, by Doreen Hoerold & Dr Niall Pender, under supervision of Professor Ian Robertson.

Full Name: _____

Signed _____

Date _____

For further questions, please contact:

Doreen Hoerold
Postgraduate Researcher
Department of Psychology & Institute of Neuroscience
Trinity College Dublin

Tel: 01 896 8405
Email: hoeroldd@tcd.ie

Patient Demographic Data

Patient ID	Gender	Age	Years of Education	Handedness
		LF Group		
008 OC	Male	53	20	Right
016 MF	Female	37	14	Right
047 PC	Male	54	10	Right
115 BD	Male	43	22	Right
239 BM	Female	62	10	Right
291 JOR	Female	32	11	Right
348 RS	Female	42	13	Right
352 OB	Male	32	15	Right
355 DJ	Male	58	8	Right
356 JD	Male	48	12	Right
360 JOR	Female	42	15	Right
363 BMG	Female	56	12	Right
		RF Group		
021 PH	Male	56	15	Right
090 BBD	Female	47	15	Right
164 MH	Male	20	14	Right
169 JW	Male	47	16	Right
216 AMC	Female	53	15	Right
335 JB	Male	40	17	Left
346 PF	Male	23	18	Right
350CH	Female	51	13	Right
353 SK	Female	37	13	Right
359 MS	Female	57	18	Right
361 KG	Male	30	19	Right
362 AB	Male	45	11	Right
364 AP	Male	64	11	Left

		LNF Group		
002 CFB	Female	50	14	Right
049 GC	Female	45	15	Right
055 CK	Female	58	12	Right
152 BG	Male	59	16	Right
161 CG	Female	36	20	Right
166 JC	Male	37	15	Right
170 PH	Female	52	18	Right
259 SM	Female	34	14	Left
266 VM	Female	52	9	Right
328 SW	Male	21	16	Ambidextrous
334 MU	Male	50	15	Left
336 PC	Male	50	18	Right
338 GC	Female	47	17	Right
339 MF	Male	42	13	Right
340 CE	Female	23	17	Right
344 SR	Male	52	17	Right
345 AP	Male	56	26	Right
347 AA	Female	26	18	Right
		RNF Group		
046 AB	Male	65	13	Left
066 GON	Female	22	14	Right
086 CB	Female	31	14	Right
088 WB	Male	49	8	Right
162 PH	Female	43	20	Right
261 MM	Male	35	12	Right
337 CC	Female	30	18	Right
341 GC	Female	53	18	Right
342 MK	Female	30	9	Left
343 GF	Male	36	10	Left
349 MON	Male	47	11	Right
351 EM	Male	21	15	Right
354 EQ	Female	45	17	Right
358 EB	Male	62	17	Right

HAD Scale

Read each item and place a firm tick in the box opposite the reply which comes closest to how you have been feeling in the past week. Don't take too long over your replies: your immediate reaction to each item will probably be more accurate than a long thought-out response.

1. I feel tense or 'wound up'.

- Most of the time ☐
- A lot of the time ☐
- Time to time, Occasionally ☐
- Not at all ☐

2. I still enjoy the things I used to enjoy.

- Definitely as much ☐
- Not quite so much ☐
- Only a little ☐
- Hardly at all ☐

3. I get a sort of frightened feeling as if something awful is about to happen.

- Very definitely and quite badly ☐
- Yes, but not too badly ☐
- A little, but it doesn't worry me ☐
- Not at all ☐

4. I can laugh and see the funny side of things.

- As much as I always could ☐
- Not quite so much now ☐
- Definitely not so much now ☐
- Not at all ☐

5. Worrying thoughts go through my mind.

- A great deal of the time ☐
- A lot of the time ☐
- From time to time but not often ☐
- Only occasionally ☐

6. I feel cheerful.

- Not at all ☐
- Not often ☐
- Sometimes ☐
- Most of the time ☐

7. I can sit at ease and feel relaxed.

- Definitely ☐
- Usually ☐
- Not often ☐
- Not at all ☐

8. I feel as if I am slowed down.

- Nearly all the time ☐
- Very often ☐
- Sometimes ☐
- Not at all ☐

9. I get a sort of frightened feeling like 'butterflies' in the stomach.

- Not at all ☐
- Occasionally ☐
- Quite often ☐
- Very often ☐

10. I have lost interest in my appearance.

- Definitely ☐
- I don't take as much care as I should ☐
- I may not take quite as much care ☐
- I take just as much care as ever ☐

11. I feel restless as if I have to be on the move.

- Very much indeed ☐
- Quite a lot ☐
- Not very much ☐
- Not at all ☐

12. I look forward with enjoyment to things.

- As much as ever I did ☐
- Rather less than I used to ☐
- Definitely less than I used to ☐
- Hardly at all ☐

13. I get sudden feelings of panic.

- Very often indeed ☐
- Quite often ☐
- Not very often ☐
- Not at all ☐

14. I can enjoy a good book or radio or TV programme.

- Often ☐
- Sometimes ☐
- Not often ☐
- Very seldom ☐

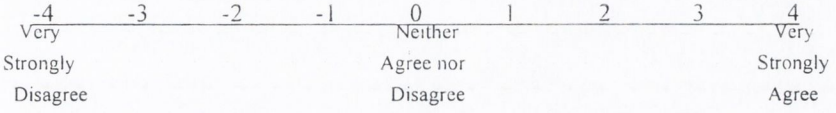
MET

Date: _____

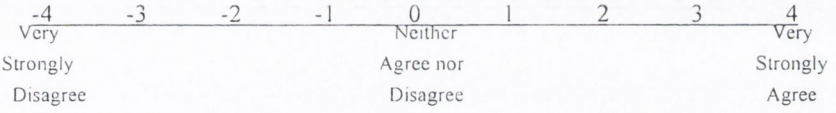
Name:_____ **Age:**_____ **Sex:**_____

Please read each item and circle the number that comes closest to how you feel.

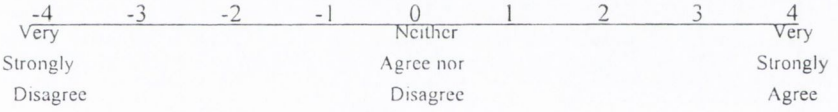
1. It makes me sad to see a lonely stranger in a group.



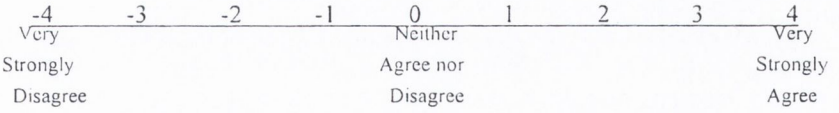
2. People make too much of the feelings and sensitivity of animals.



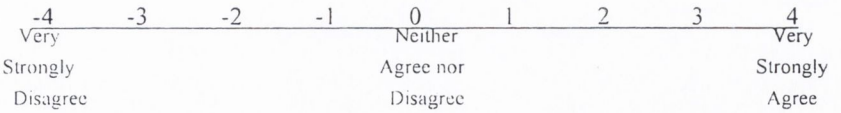
3. I often find public displays of affection annoying.



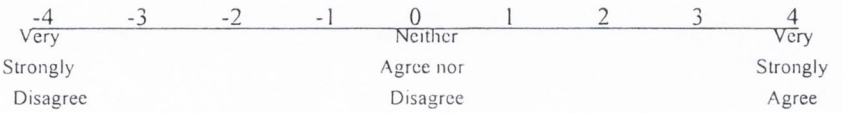
4. I am annoyed by unhappy people who are just sorry for themselves.



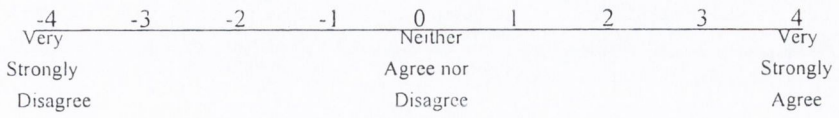
5. I become nervous if others around me seem to be nervous.



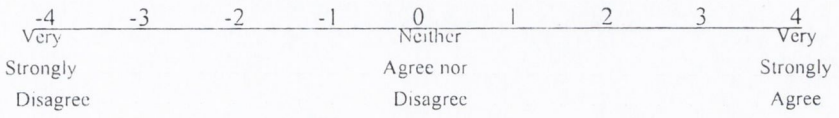
6. I find it silly for people to cry out of happiness.



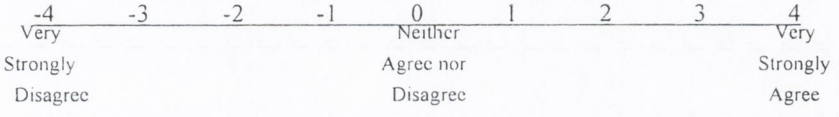
7. I tend to get emotionally involved with a friend's problems.



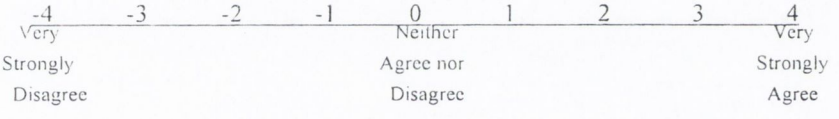
8. Sometimes the words of a love song can move me deeply.



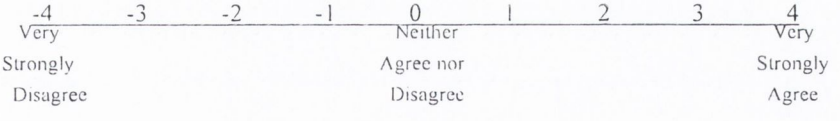
9. I tend to lose control when I am bringing bad news to people.



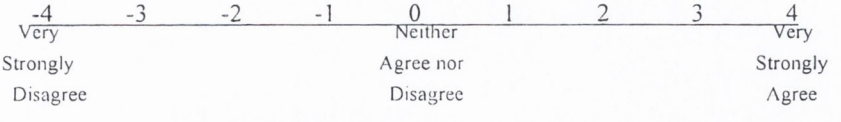
10. The people around me have a great influence on my moods.



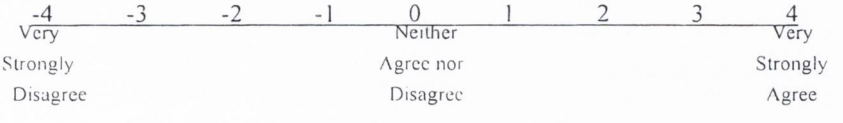
11. Most foreigners I have met seemed cold and unemotional.



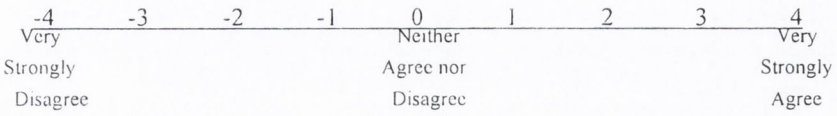
12. I would rather be a social worker than work in a job in a training centre.



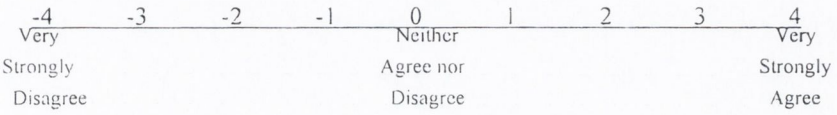
13. I don't get upset just because a friend is acting upset.



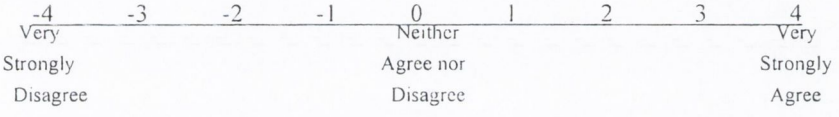
14. I like to watch people open presents.



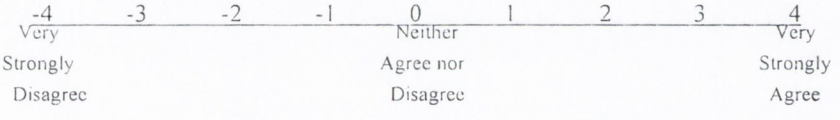
15. Lonely people are probably unfriendly.



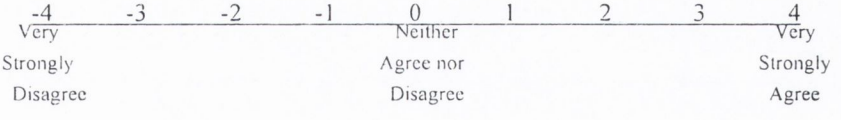
16. Seeing people cry upsets me.



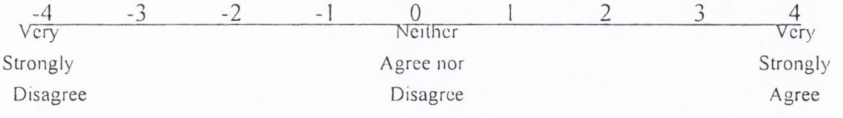
17. Some songs make me happy.



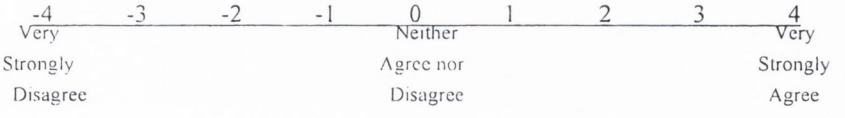
18. I really get involved with the feelings of the characters in a novel.



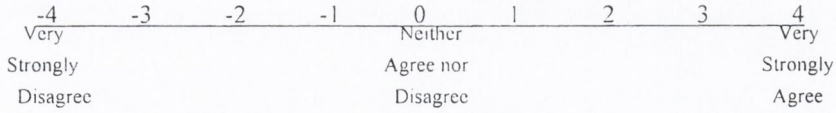
19. I get very angry when I see someone being ill-treated.



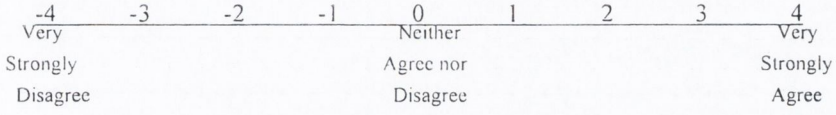
20. I am able to remain calm even though those around me worry.



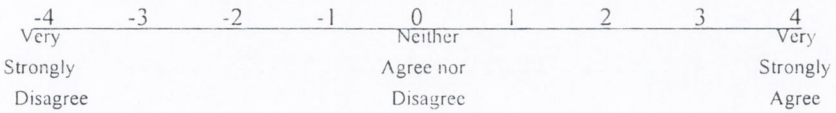
21. When a friend starts to talk about his/her problems, I try to steer the conversation to something else.



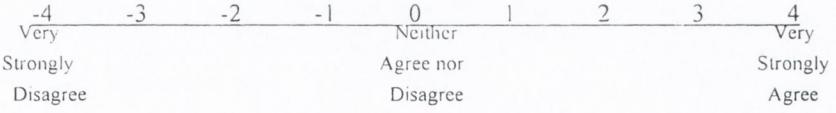
22. Another's laughter is not catching for me.



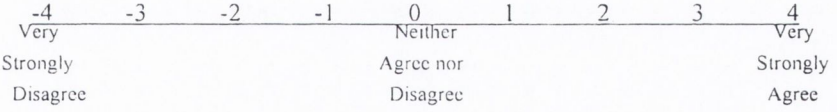
23. Sometimes at the cinema I am amused by the amount of crying and sniffling around me.



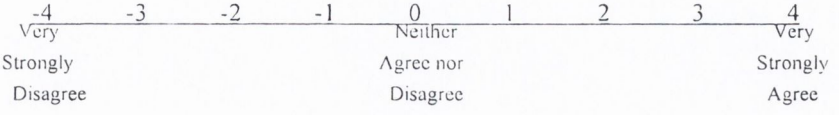
24. I am able to make decisions without being influenced by people's feelings.



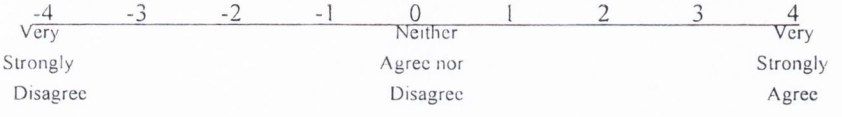
25. I cannot continue to feel ok if people around me are depressed.



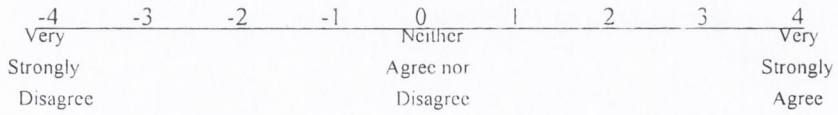
26. It is hard for me to see how some things upset people so much.



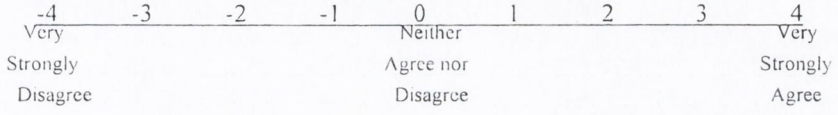
27. I am very upset when I see an animal in pain.



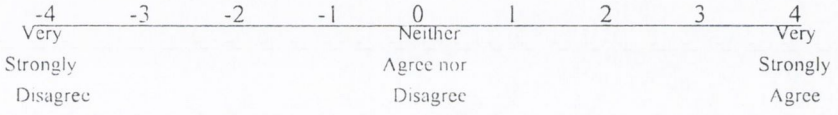
28. Becoming involved in books or films is silly.



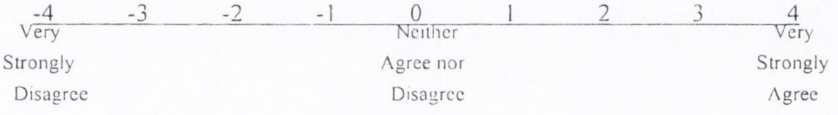
29. It upsets me to see helpless people.



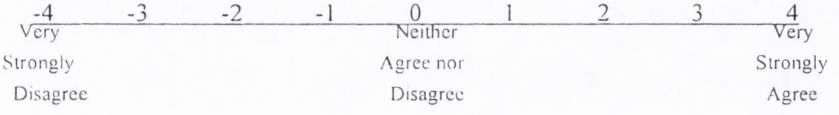
30. I become more irritated than sympathetic when I see someone's tears.



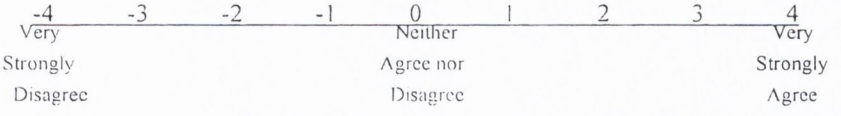
31. I become very involved when I watch a film.



32. I often find that I can remain cool in spite of the excitement around me.



33. Little children sometimes cry for no apparent reason.



CFQ

Name ..... Date.....

.....

The following questions are about minor mistakes which everyone makes from time to time, but some of which happen more often than others. We want to know how often these things have happened to you in the last six months. Please circle the appropriate number.

	Very often	Quite often	Occasio-nally	Very rarely	Never
Do you read something and find you haven't been thinking about it and must read it again?	4	3	2	1	0
Do you find you forget why you went from one part of the house to the other?	4	3	2	1	0
Do you fail to notice signposts on the road?	4	3	2	1	0
Do you find you confuse right and left when giving directions?	4	3	2	1	0
Do you bump into people?	4	3	2	1	0
Do you find you forget whether you've turned off a light or a fire or locked the door?	4	3	2	1	0
Do you fail to listen to people's names when you are meeting them?	4	3	2	1	0
Do you say something and realise afterwards that it might be taken as insulting?	4	3	2	1	0
Do you fail to hear people speaking to you when you are doing something else?	4	3	2	1	0
Do you lose your temper and regret it?	4	3	2	1	0
Do you leave important letters unanswered for days?	4	3	2	1	0
Do you find you forget which way to turn on a road you know well but rarely use?	4	3	2	1	0
Do you fail to see what you want in a supermarket (although it's there)?	4	3	2	1	0

Do you find yourself suddenly wondering whether you've used a word correctly?	4	3	2	1	0
Do you have trouble making up your mind?	4	3	2	1	0
Do you find you forget appointments?	4	3	2	1	0
Do you forget where you put something like a newspaper or a book?	4	3	2	1	0
Do you find you accidentally throw away the thing you want and keep what you meant to throw away as in the example of throwing away the matchbox and putting the used match in your pocket?	4	3	2	1	0
Do you daydream when you ought to be listening to something?	4	3	2	1	0
Do you find you forget people's names?	4	3	2	1	0
Do you start doing one thing at home and get distracted into doing something else (unintentionally)?	4	3	2	1	0
Do you find you can't quite remember something although it's 'on the tip of your tongue'?	4	3	2	1	0
Do you find you forget what you came to the shops to buy?	4	3	2	1	0
Do you drop things?	4	3	2	1	0
Do you find you can't think of anything to say?	4	3	2	1	0

CFQ (For Others)

The questions given below are about mistakes and difficulties which everybody has from time to time. We would like you to think of a recent two-month period when _____ has shown any of these difficulties. After each question, please tick only one of five possible answers. Please make sure you read them carefully.

During the last two months _____ seemed to be:

	Very often	Quite often	Occasio-nally	Very rarely	Never
Absentminded, that is making mistakes in what he/she is doing because he/she is thinking of something else?	4	3	2	1	0
Finding it difficult to concentrate on anything because his/her attention tends to wander from one thing to another ?	4	3	2	1	0
Forgetful, such as forgetting where he/she has put things, or about appointments, or about what he/she has done?	4	3	2	1	0
Busy thinking about his/her own affairs, and so not noticing what is going on around him/her ?	4	3	2	1	0
Clumsy, for example dropping things or bumping into people ?	4	3	2	1	0
Having difficulty in making up his/her mind ?	4	3	2	1	0
Disorganised, that is, getting into a muddle when doing something because of lack of planning or concentration ?	4	3	2	1	0
Getting unduly cross about minor matters ?	4	3	2	1	0

Patient Competency Rating
(Patient's Form)

Source: Prigatano, G.P. and Others (1986). Neuropsychological Rehabilitation After Brain Injury. Baltimore: John Hopkins University Press.

Identifying Information

Patient's Name: _____

Date: _____

Instructions

The following is a questionnaire that asks you to judge your ability to do a variety of very practical skills. Some of the questions may not apply directly to things you often do, but you are asked to complete each question as if it were something you "had to do". On each question, you should judge how easy or difficult a particular activity is for you and mark the appropriate space.

Competency Rating

1	2	3	4	5
Can't do	Very difficult to do	Can do with some difficulty	Fairly easy to do	Can do with ease

____ 1. How much of a problem do I have in preparing my own meals ?

____ 2. How much of a problem do I have in dressing myself ?

____ 3. How much of a problem do I have in taking care of my personal hygiene ?

____ 4. How much of a problem do I have in washing the dishes ?

____ 5. How much of a problem do I have in doing the laundry ?

____ 6. How much of a problem do I have in taking care of my finances?

____ 7. How much of a problem do I have in keeping appointments on time ?

1 Can't do	2 Very difficult to do	3 Can do with some difficulty	4 Fairly easy to do	5 Can do with ease

____ 8. How much of a problem do I have in starting conversation in a group ?

____ 9. How much of a problem do I have in staying involved in work activities even when bored or tired ?

____ 10. How much of a problem do I have in remembering what I had for dinner last night ?

____ 11. How much of a problem do I have in remembering names of people I see often ?

____ 12. How much of a problem do I have in remembering my daily schedule ?

____ 13. How much of a problem do I have in remembering important things I must do ?

____ 14. How much of a problem would I have driving a car if I had to ?

____ 15. How much of a problem do I have in getting help when I'm confused ?

____ 16. How much of a problem do I have in adjusting to unexpected changes ?

____ 17. How much of a problem do I have in handling arguments with people I know well ?

____ 18. How much of a problem do I have in accepting criticism from other people ?

____ 19. How much of a problem do I have in controlling crying ?

____ 20. How much of a problem do I have in acting appropriately around friends ?

____ 21. How much of a problem do I have in showing affection to people ?

____ 22. How much of a problem do I have in participating in group activities ?

1	2	3	4	5
Can't do	Very difficult to do	Can do with some difficulty	Fairly easy to do	Can do with ease

____ 23. How much of a problem do I have in recognizing when something I say or do has upset someone else ?

____ 24. How much of a problem do I have in scheduling daily activities ?

____ 25. How much of a problem do I have in understanding new instructions ?

____ 26. How much of a problem do I have in consistently meeting my daily responsibilities ?

____ 27. How much of a problem do I have in controlling my temper when something upsets me ?

____ 28. How much of a problem do I have in keeping from being depressed ?

____ 29. How much of a problem do I have in keeping my emotions from affecting my ability to go about the day's activity ?

____ 30. How much of a problem do I have in controlling my laughter ?

Patient Competency Rating
(Relative's Form)

Source: Prigatano, G.P. and Others (1986). Neuropsychological Rehabilitation After Brain Injury. Baltimore: John Hopkins University Press.

Identifying Information

Patient's Name: _____

Date: _____

Informant's relationship to patient (circle one):

1. Mother
2. Father
3. Spouse
4. Child
5. Sibling
6. Grandparent
7. Aunt or uncle
8. Niece or nephew
9. Cousin
10. Friend
11. In-Law
12. Ward attendant
13. Other _____

Sex of informant:

Male_____
Female_____

How well is informant acquainted with patient's behavior ?

1. Hardly at all
2. Not so well
3. Fairly well
4. Pretty well
5. Very well

Instructions

The following is a questionnaire that asks you to judge this person's ability to do a variety of very practical skills. Some of the questions may not apply directly to things they often do, but you are asked to complete each question as if it were something they "had to do". On each question, you should judge how easy or difficult a particular activity is for them and mark the appropriate space.

Competency Rating

1	2	3	4	5
Can't do	Very difficult to do	Can do with some difficulty	Fairly easy to do	Can do with ease

____ 1. How much of a problem do they have in preparing their own meals ?

____ 2. How much of a problem do they have in dressing themselves ?

____ 3. How much of a problem do they have in taking care of their personal hygiene ?

____ 4. How much of a problem do they have in washing the dishes ?

____ 5. How much of a problem do they have in doing the laundry ?

____ 6. How much of a problem do they have in taking care of their finances?

____ 7. How much of a problem do they have in keeping appointments on time ?

____ 8. How much of a problem do they have in starting conversation in a group ?

____ 9. How much of a problem do they have in staying involved in work activities even when bored or tired ?

____ 10. How much of a problem do they have in remembering what they had for dinner last night ?

____ 11. How much of a problem do they have in remembering names of people they see often ?

____ 12. How much of a problem do they have in remembering their daily schedule ?

____ 13. How much of a problem do they have in remembering important things they must do ?

____ 14. How much of a problem would they have driving a car if they had to ?

1 Can't do	2 Very difficult to do	3 Can do with some difficulty	4 Fairly easy to do	5 Can do with ease

____ 15. How much of a problem do they have in getting help when they're confused ?

____ 16. How much of a problem do they have in adjusting to unexpected changes ?

____ 17. How much of a problem do they have in handling arguments with people they know well ?

____ 18. How much of a problem do they have in accepting criticism from other people ?

____ 19. How much of a problem do they have in controlling crying ?

____ 20. How much of a problem do they have in acting appropriately around friends ?

____ 21. How much of a problem do they have in showing affection to people ?

____ 22. How much of a problem do they have in participating in group activities ?

____ 23. How much of a problem do they have in recognizing when something they say or do has upset someone else ?

____ 24. How much of a problem do they have in scheduling daily activities ?

____ 25. How much of a problem do they have in understanding new instructions ?

____ 26. How much of a problem do they have in consistently meeting their daily responsibilities ?

____ 27. How much of a problem do they have in controlling their temper when something upsets them ?

____ 28. How much of a problem do they have in keeping from being depressed ?

1	2	3	4	5
Can't do	Very difficult to do	Can do with some difficulty	Fairly easy to do	Can do with ease

____ 29. How much of a problem do they have in keeping their emotions from affecting their ability to go about the day's activity ?

____ 30. How much of a problem do they have in controlling their laughter ?

Example of SOPT Stimuli

