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An Investigation of Error Awareness in Healthy Ageing and a Non-invasive Approach to its Amelioration

by

Siobhán Harty

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

2014

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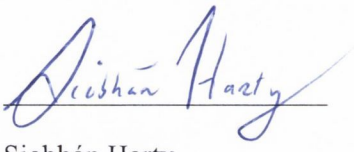

Siobhán Harty

Date

7/04/2015

Summary

Population ageing has become a global phenomenon. This demographic change flags the remarkable developments made by humanity in recent history, but it also constitutes one of the most challenging problems for contemporary society, as coincident with ever increasing life expectancies, are increasing rates of age-related cognitive decline. Non-pathological ageing is accompanied by several cognitive and brain changes that manifest in multiple dimensions. On the one hand, older adults have improved regulation of emotion, better vocabulary, better culture-related knowledge, and have better life satisfaction, compared to younger adults. On the other, they have reduced acuity of the senses, they require more time to both process, and respond to, sensory information, and invariably, they undergo declines in a number of other important physical and cognitive capacities. As the deterioration of older adults' cognitive capacities begins to occur, the ability to monitor and evaluate the success of their cognitive processes is of paramount importance for detecting errors, and calibrating their daily activities to suit their strengths and weaknesses. Yet, the extent to which these monitoring processes are affected by the natural ageing process has rarely been considered in the literature. The purpose of the present work is to contribute to this knowledge base by exploring two main themes. The first of these concerns examining the extent to which the capacity for self-awareness is disrupted by the natural ageing process. The second part of this thesis aims to assess the viability of tDCS as a tool for increasing our understanding of, as well as ameliorating, self-awareness in older adults. Chapter 1 begins by reviewing the literature that provides the theoretical basis for the work within this thesis.

Chapter 2 employed a multi-domain assessment of self-awareness in healthy older adults and young adult controls. Convergent data from a laboratory measure of online error awareness and real-world measures of awareness of attentional control and memory functioning indicated that older adults have significantly reduced awareness of cognitive functioning, relative to young adults. These group differences could not be attributed to a range of factors that were controlled for, including speed of cognitive response, speed of motor response, anxiety, depression or pathology-related impairments.

The main aim of Chapter 3 was to provide a more mechanistic account of older adults' awareness deficits. The recent conceptualisation of the emergence of error awareness as a second-order decision process has offered a valuable mechanistic model that makes clear empirically verifiable predictions regarding both error awareness and the underlying neural implementation. Electroencephalography (EEG) research in turn has identified candidate neural signatures, namely, error-related medial-frontal (MF) theta oscillatory power and the

error positivity (Pe), that bear the key characteristics of signals predicted by these models. Heeding the potential for these signals to shed light on the mechanistic underpinnings of awareness deficits, Chapter 3 constituted an interrogation of MF theta power and the Pe in healthy older adults and young adult controls during the performance of a previously validated error awareness task. Primarily, the results from Chapter 3 provided basis for inferring that older adults awareness deficits may be attributable to declines in the ability to encode error evidence, as indexed by MF theta power, and in the subsequent accumulation of that evidence during second-order decision making, indexed by the Pe.

Chapters 4 to 6 form the second major section of this thesis. Chapter 4 reviews the evidence that the non-invasive brain stimulation technique, transcranial direct current stimulation (tDCS), may represent a valuable tool for a wide array of both scientific and clinical purposes. Chapter 5 subsequently employs tDCS with the dual goals of determining whether right dorsolateral prefrontal cortex (dlPFC) plays a causal role in supporting error awareness and assessing the potential of tDCS to remediate error awareness deficits in older age. The influence of electrode location (right vs left dlPFC) and current polarity (anodal vs cathodal) is tested in a series of separate single-blind, sham-controlled cross over experiments, each including 24 healthy older adults. Anodal tDCS over right, but not left, dlPFC was associated with a significant increase in error awareness which could not be accounted for by changes in accuracy, slower response times, the neuromodulatory influence of the reference electrode, or expectancy effects due to greater somatic sensation. This result was recapitulated in a separate replication experiment. Chapter 5 thus provided novel evidence to support the hypothesis that right lateralised dlPFC structures play a critical role in mediating awareness of cognitive functioning, which has been strongly suggested by an extensive literature on the phenomenon in clinical populations.

Chapter 6 follows on directly from Chapter 5 by acquiring EEG data concurrent to tDCS and also investigating whether the effects of tDCS persisted beyond the stimulation period. The co-registration of EEG and tDCS provided both a window into the neurophysiological correlates of the tDCS-induced improvements in error awareness and a means to test the prediction that the application of tDCS over right dlPFC would be associated with neural network effects that involved secondary modulation of the pMFC, the putative source of MF theta oscillations. As predicted, tDCS-induced improvements in error awareness were accompanied by enhanced MF theta power, in addition to both a steeper and earlier peak of the Pe.

Finally, Chapter 7 provides a discussion of the implications of this work and future challenges in this direction.

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List of Publications

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Chapter 5:

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Murphy, P.R., Robertson, I.H., **Harty, S.,** & O'Connell, R.G. (under review). Signals for second-order decision making in the human brain.

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Harty, S., Robertson, I.H., & O'Connell, R.G. (2013). Transcranial Direct Current Stimulation over Right Dorsolateral Prefrontal Cortex Enhances Error Awareness in Older Adults. *MCC Neural circuits for adaptive control of behaviour.* Paris.

Harty, S., Robertson, I.H., & O'Connell, R.G. (2013). Error Awareness Deficits in Older Adults: Evidence from Event-Related Potentials and Transcranial Direct Current Stimulation. *Society for Psychophysiological Research.* Florence.

Harty, S., Robertson, I.H., Hester, R., & O'Connell, R.G. (2012). Normal aging is associated with a decline in the ability to consciously self-monitor cognitive performance. *Society for Neuroscience*. New Orleans.

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Chapter 1: Conceptual Background

1.1 Introduction

By the year 2075, more than 50% of the European population will be aged 60 or more, and there will be a three-fold increase in individuals aged 80 or more, relative to the present day. It is important that our society prepares for this demographic change and endeavours to enable older adults to optimise their quality of life and autonomy for as long as possible. To the extent that age-related cognitive decline is one of the biggest threats to independent living and well-being for this cohort, the field of cognitive neuroscience is arguably the discipline with the most potential to help in this regard. Non-pathological ageing is accompanied by several cognitive and brain changes that are a product of the natural ageing process, one's environment, and one's ability to compensate for them. These changes become evident in multiple cognitive dimensions. On the one hand, older adults have improved regulation of emotion, better vocabulary, better culture-related knowledge, and have better life satisfaction, compared to younger adults. On the other, they have reduced acuity of the senses, they require more time to both process, and respond to, sensory information, and invariably, they undergo declines in a number of other important physical and cognitive capacities. As the deterioration of older adults' cognitive capacities begins to occur, the ability to monitor and evaluate the success of their cognitive processes is of paramount importance for detecting errors, and calibrating their daily activities to suit their strengths and weaknesses. Yet, the extent to which these metacognitive monitoring processes are affected by the natural ageing process has rarely been considered in the literature. A wealth of evidence from research on clinical populations indicates that metacognitive capacities are highly susceptible to disruption in several diverse neurological conditions, particularly those with damage to right frontal regions. Considering there is much evidence to suggest that the frontal lobe is one of the brain regions that undergoes the most extensive age-related changes (Dempster, 1992; Mosocovitch & Wincour, 1992; Raz, Gunning, Head

et al., 1997; West, 1996), the question follows whether metacognitive capacities are also vulnerable to disruption due to the natural ageing process.

The aim of this chapter is to provide the conceptual background to the empirical work presented within this thesis, however, the literature on neural plasticity and non-invasive brain stimulation, which is particularly pertinent to the latter empirical chapters (5 and 6), will not be covered in detail until Chapter 4. The present chapter is organised in six main sections. In the proceeding section, an overview of different perspectives on ageing at the neuropsychological and neurobiological level is provided. The third section introduces the topic of metacognition and draws on the clinical literature surrounding anosognosia to highlight the importance of metacognitive abilities, how they are measured, and what is known about their neuropsychological and neuroanatomical bases. The fourth and fifth sections provide more focussed reviews of the cognitive neuroscience literature on performance monitoring and conscious error awareness, respectively, which in the context of this thesis, are hypothesised to be critical to the accuracy of many metacognitive abilities. The sixth and final section provides an overall summary and an outline of the objectives of this thesis.

1.2 Age-Related Cognitive and Cerebral Decline

A robust, and positive, finding to emerge from cognitive ageing research is that age-related losses are not necessarily seen across all cognitive functions. Patterns of relative preservation versus decline are usually particularly apparent for what are known as crystallized versus fluid intelligence domains (Horn & Cattell, 1967). These two clusters of intellectual abilities have also been discussed in terms of the *pragmatics* and *mechanics* of cognition (Baltes, Lindenberger, & Staudinger, 1998). The former constitutes a culture-related knowledge base that is accumulated through experience, whereas the latter constitutes content-free information processing that relies on fundamental biological processes, and therefore mainly on the integrity of the central nervous system. Both cross-sectional (Lindenberger & Baltes, 1995) and longitudinal studies (Schaie 1996; 2005) have indicated that processes in the fluid intelligence domain begin to decline from middle adulthood on, whereas capacities in the crystallized domain improve from childhood right through to adulthood and then either remain stable or continue to improve until very late in life. As such many authors have described cognitive ageing as a multi-dimensional and multi-directional process.

1.2.1 Perspectives on cognitive ageing at the behavioural level

Many theories have been proposed to explain age-related declines and individual differences in cognitive functioning. Given that it is not within the objectives of this thesis to test any particular theory of cognitive ageing, this section provides a brief overview, as opposed to a comprehensive review, of the main perspectives on cognitive ageing at the behavioural level. This section is then followed by an overview of literature on cognitive ageing at the neurobiological level.

The cognitive control hypothesis

Common to many of the processes that witness age-related declines is a reliance on cognitive control. Cognitive control is critical to a range of higher order processes that allow for the regulation of sensory information and behaviour in accordance with one's goals. These processes include monitoring, sequencing, initiation of action, inhibiting pre-potent responses, formulating goals, focusing attention and generating response alternatives (Fuster, 2000; Miller, 2000; Miller & Cohen, 2000). These higher order control processes are also frequently referred to as executive functions (Baddeley, 1986; Norman & Shallice, 1986; Shallice, 1998), and are predominantly mediated by the frontal lobes. Age-related differences are consistently observed on tasks that place high demands on cognitive control, including working memory (Borella, Ghisletta, & de Ribaupierre, 2011; Hasher & Zacks, 1988; Salthouse, 1994), attention (McAvinue; McDowd, 1986; Milham, Erickson, Banich et al., 2002; Hawkins, Kramer, & Capaldi, 1992; West, 2004), multi-tasking (Clapp, Rubens, Sabharwal & Gazzaley, 2011; Jimura & Braver, 2010), as well as episodic and source memory (Craik, Morris, Morris, & Loewen, 1990). In contrast, older adults' performance on measures of non-declarative or implicit memory, which are believed to rely on more automatic and less control demanding processes, has been found to be largely age invariant (Bergerbest, Gabrieli, Whitfield-Gabrieli et al., 2009; Fleischman & Gabrieli, 1998; Light & Singh, 1987; La Voie & Light, 1994). Such observations have prompted many authors to propose that age-related cognitive decline may arise from impaired or inefficient deployment of cognitive control processes due to age-related degeneration of frontal lobe structures (Braver & Barch, 2002; Crawford, Bryan, Luscez, Obonsawin, & Stewart, 2000; Glisky, 2007; Greenwood, 2000; West, 2000; Rodriguez-Aranda & Sundet, 2006). This general idea has been variously termed the "cognitive control hypothesis" (West, 1996; 2000; Gallo, Bell, Beier, & Schacter, 2006; Koutstaal, 2006) "frontal lobe hypothesis" (West, 2000), "frontal ageing hypothesis" (Greenwood, 2000), "executive decline hypothesis" (Crawford et al., 2000), and "frontal hypothesis" (Rodríguez-Aranda & Sundet, 2006). In support of this idea

executive functions have been found to mediate the relationship between age and general cognitive capacities (Salthouse, Atkinson, & Berish, 2003) and have explained age-related differences in learning and memory (Brooks, Kempe, & Sionova, 2006; Crawford et al., 2000). Furthermore, when young and older adults' performance on putative tests of frontal, temporal, and parietal functions were compared, the strongest correlation to emerge was between age and frontal measures, with advancing age being predictive of decreasing performance on frontal lobe measures (Mittenberg, Seidenberg, O'Leary, & Digioulo, 1989).

The processing-speed hypothesis

Salthouse (1996) has argued that age-related deficits in controlled processing are secondary to a generalised reduction in the processing speed of underlying cognitive operations. Behavioural slowing has long been considered a primary concomitant of the ageing process. Christensen & Kumar (2003) have suggested that processing speed peaks in the early 20s and then declines by approximately 20% by the age of 40, and by up to 40-60% by the age of 80. Age-related declines in processing speed have been attributed to a general slowing of information processing (Birren & Fisher, 1995) or increased neural noise (Welford, 1965) within the central nervous system with advancing age. In support of the processing-speed theory it has been observed that age differences on several capacities in the fluid domain, such as abstract reasoning, working memory, and problem solving were attenuated after statistically controlling for processing speed (Bors & Farrin, 1995; Salthouse, 1996; Salthouse & Babcock, 1991; Zimprich & Martin, 2002). Speed of processing was also found to be the main predictor of age-related changes in memory and spatial ability (Finkel & McGue, 1993).

The inhibitory deficit hypothesis

Hasher and Zacks (1988) advanced that a selective deficit in inhibitory control processes may constitute a global cognitive ageing phenomenon. More specifically, this theory assumes that in order for goals to be fulfilled effectively, automated responses to non-goal relevant information need to be suppressed. However, age-related reductions in inhibitory control enable non-goal relevant information to vie for attentional resources, which results in greater distractibility, slowed and error-prone behaviour, and greater forgetting rates (Lustig, Hasher & Zacks, 2007; Hasher & Zacks, 1998). Age-related declines in inhibitory control and increased susceptibility to distractors have been found to explain a considerable proportion of age-related variance in working memory capacity (Hasher, Zacks,

& May, 1999). In a more recent study, both processing speed and inhibition were identified as independent mediators of age differences in working memory capacity (Borella, Ghisletta, & de Ribaupierre, 2011).

Dedifferentiation and cognitive permeation

Many studies have reported that the statistical correspondence between sensory and sensorimotor abilities such as vision, hearing, balance, and gait, and intellectual abilities in both fluid and the crystallized domain is significantly greater in older adults than in young adults (e.g. Baltes & Mayer, 1999). Moreover, it has been found that for older adults sensory functioning is a stronger predictor of capacities in the fluid domain than a comprehensive set of sociobiographic factors (Baltes & Lindenberger, 1997). This apparent loss of domain specificity with increasing age has been termed "dedifferentiation."

A number of authors have proposed that this apparent dedifferentiation of functions may be attributable to sensory and sensorimotor functions placing greater demands on attentional control resources. This has become known as the cognitive permeation hypothesis (e.g. Lindenberger, Marsiske, & Baltes, 2000; Schäfer, Huxhold, Lindenberger, 2006). According to this hypothesis, resource overlap and competition amongst domains increases with advancing age, and compensation in the form of resource allocation trade-offs become more frequent (Li & Lindernberger, 2002; Schäfer et al., 2006). In accord with this, Li et al. (Li, Lindenberger, Freund & Baltes, 2001) have shown that balance during walking was preserved at the expense of performance of a simultaneously executed cognitive task. Such findings suggest that age-related declines in cognitive domains could be attributable to increased allocation of attentional resources to processes that were previously automated.

Cognitive Reserve

Another important conceptual framework labelled 'cognitive reserve,' concerns how older adults may be able to draw on a pool of accumulated resources to maintain cognitive function. The notion of cognitive reserve emerged from recurrent observations that levels of cognitive impairment did not always manifest to the extent that would be expected from a given brain pathology (Stern, 2002). For instance, Katzman et al. (Katzman, Terry, DeTeresa et al., 1998) have reported that older adults can be cognitively intact up until they die, but exhibit advanced AD-related cerebral pathology at post-mortem. Such discrepancies have also been observed in a range of other conditions including stroke (Ojala-Oksala, Jokinen, Kopsi et al., 2012) and traumatic brain injury (TBI; Kesler, Adams, Blasey, & Bigler, 2003).

This apparent elevation of threshold for cognitive impairment appears to be promoted by factors such as high levels of education, occupational complexity, and participation in cognitively stimulating leisure activities (Mortimer, 1997). It has been proposed that cognitive reserve may mediate individual differences in non-pathological cognitive ageing by fostering more efficient utilisation of brain networks or an enhanced ability to recruit alternate networks (Stern, 2002).

Summary

The natural ageing process is associated with myriad cognitive changes. Some of the most pronounced and consistently reported are on tasks that challenge cognitive control processes and working memory, or that require long term working memory (Hedden & Gabrieli, 2004; Piguet & Corkin, 2007). Several hypotheses about cognitive ageing at the behavioural level have been advanced, and each hypothesis described above continues to feature prominently in recent literature. However, it is difficult to arbitrate between these theories in the absence of neural evidence. The next sub-section will outline how the increasing availability of neuroimaging technologies has provided important new insights into the relationship between age-related changes in brain structure and function, and concomitant changes in cognitive abilities.

1.2.2 Perspectives on cognitive ageing at the neurobiological level

In the same way that ageing does not have an equal impact on all cognitive domains, ageing does not result in a general deterioration of the brain. Rather, the ageing brain is characterised by a 'patchwork pattern of differential declines and relative preservation,' not only at the structural level, but also at the functional level (Raz, 2000).

Structural changes

Grey matter integrity

Magnetic resonance imaging (MRI) based studies consistently show a global age-related reduction in grey matter volumes, but considerable regional differences exist in terms of the magnitude and relative rate of change. In a longitudinal study, which spanned five years, Raz et al. (Raz, Lindenberger, Rodrigue et al., 2005) found a significant negative association between age and volume in the lateral prefrontal cortex, the orbitofrontal cortex, the cerebellum, the caudate and the hippocampus. These associations were found to be stronger

after five years for the prefrontal regions, the cerebellum, the caudate and the hippocampus, indicating age-related accelerations in the shrinkage of these regions. Conversely, volumes in areas such as the primary visual cortex, the fusiform cortex and the inferior parietal lobes were not significantly associated with age, and there was no change in these associations over the course of five years. Several other studies using a variety of methods have reported similar findings, and in particular, an ever-growing literature documents the most dramatic age-related grey matter volume losses in the prefrontal cortex (Allen et al. 2005; Bartzokis et al., 2001; Heddin & Gabrieli, 2004; Pfefferbaum et al., 1994; Raz, 2004; Salat et al., 2005; Walhovd et al., 2005).

White matter integrity

Post-mortem studies, as well as diffusion-tensor imaging (DTI)-based studies indicate that the natural ageing process is also associated with a deterioration of white matter integrity (Bartzokis et al., 2003; Double et al., 1996; Peters, 2002; Piguet et al., 2009). Similar to grey matter volume, declines in white matter integrity are widespread, but again tend to be most pronounced in anterior areas, including the genu of the corpus collosum, and the white matter underlying the prefrontal (PFC; Ardekani, Kumar, Bartzokis, & Sinha., 2007; Salat, Tuch, Greve et al., 2005; Sullivan & Pfefferbaum, 2006). These findings have led to the hypothesis that age-related loss in both grey matter volume and white matter integrity occurs along an anterior-to-posterior gradient (Jernigan, Trauner, Hesselink et al., 1991; Raz & Rodrigue, 2006; Salat, Tuch, Greve et al., 2005; Sowell, Petersen, Thompson et al., 2003), and is compatible with the previously described "frontal lobe hypothesis" of ageing.

Relationship between grey matter integrity loss and cognitive functioning

While these age-related patterns of neuroanatomical change have been relatively well characterised, the specific link between these, and patterns of cognitive decline remains a matter of debate. Burzynska et al. (Burzynska, Nagel, Presuschhof et al., 2012) investigated the association between grey matter volume, as indexed by MRI, and executive functioning, as indexed by performance on the Wisconsin Card Sorting Test (WCST), in young and older adults. The primary regions of interest were the lateral PFC and parietal cortices, which are known to support performance on the WCST. They found that preservation of grey matter volume was associated with better performance on the WCST, and this association was stronger for the older adult group. A number of other studies have provided similar support for an association between such cortical integrity and preservation of cognitive function. Specifically, reduced global cortical volume, and reduced volumes in the orbitofrontal cortex (OFC) and dorsolateral PFC (dlPFC) in older adults was associated

with diminished attention and executive function (Kramer, Mungas, Reed et al., 2007; Zimmerman, Brickman, Paul et al., 2006), and the volume of right PFC was inversely correlated with the number of perseverative errors that older adults made on the WCST (Gunning-Dixon & Raz, 2003). Yet, these latter authors also found that there was no association between PFC volume and age-related changes in object, spatial or verbal working memory (Gunning-Dixon & Raz, 2003), and an inverse correlation between OFC volume and working memory function has also been documented elsewhere (Salat, Kaye, & Janosky, 2002).

Relationship between white matter integrity loss and cognitive functioning

Much work has also probed the relationship between white matter integrity and age-related changes in cognitive function. Several studies have documented an association between deficits in speed of processing, executive functioning, immediate and delayed recall, as well as overall cognitive functioning, and the volume of white matter hyperintensities (WMH; Au, Massaro, Wolf, Young et al., 2006; Gunning-Dixon & Raz, 2000; Gunning-Dixon & Raz, 2003; Smith, Salat, Jeng et al., 2011; Soderlund, Nyberg, Adolfsson et al., 2003). WMH refer to white matter lesions that present as high signal intensities in T2-weighted MRI scans. They are believed to be the result of axon degeneration, axon demyleniation, and other microscopic structural changes that manifest in the white matter connective tracts of the central-nervous system as a part of the natural ageing process (Kennedy & Raz, 2009). WMH in older adults have also been associated with a diminished blood-oxygen-level-dependent (BOLD) response in PFC during episodic and working memory tasks (Nordahl, Ranganath, Yonelinas et al., 2006), and with decreased frontal lobe metabolism (DeCarli, Murphy, Tranh et al., 1995; Tullberg, Fletcher, deCarli et al., 2004). Thus both, grey matter atrophy and the degeneration of white matter integrity with advancing age are most pronounced for anterior regions such as PFC and appear to contribute to the aetiology of age-related cognitive decline.

Functional changes

Brain structural integrity, however, is only one neural determinant of differences in cognitive function among older adults. With respect to neurotransmitter modulation, the production and uptake of most, if not all, decline with increasing age (see Rehman & Masson, 2001; Backman, Nyberg, Lindenberger, Li, & Farde, 2006 for reviews). Studies of brain function using tools such as functional MRI (fMRI) and positron emission tomography (PET) have also revealed global reductions in cerebral blood flow and cerebral metabolism of glucose at rest (Meltzer, Becker, Price, & Moses-Kolko, 2003; Raz et al., 2005).

Reductions in task-induced functional activation as a function of age have also been observed, but again regional variability is extensive, and increased activation of regions is also common. The following paragraphs provide an overview of the models that have been developed to describe the patterns of functional activation that are commonly observed in older adults.

Descriptions of age-related functional changes

The first model stems from the HERA (Hemisphere Encoding Retrieval Asymmetry) model that was initially proposed to account for the lateralisation of regional recruitment in young adults during episodic memory tasks (Tulving, Kapur, Craik, Moscovitz, & Hoile, 1994), whereby left PFC is activated during memory encoding processes while right PFC is engaged in the memory retrieval processes. Studies have failed to find such lateralisation of function in older adults, however. Instead, activity in older adults has tended to be less lateralised regardless of the episodic memory processes in operation. These functional changes have been referred to as HAROLD (Hemisphere Asymmetry Reduction in OLDer adults; Cabeza, 2002; Cabeza, Grady, Nyberg et al., 1997). The HAROLD pattern has been observed in a number of functional imaging studies for not only episodic memory, but also working memory, semantic memory retrieval, perception, and inhibitory control (Dixit, Gerton, Kohn, Myer-Lindenberg, & Berman, 2000; Dolcos, Rice, & Cabeza; Nielson, Langenecker, & Garavan, 2002; Reuter-Lorenz, Jonides, Smith et al., 2000). Consequently, this pattern is unlikely attributable to task demands, and has thus been regarded by many as a general feature of cognitive ageing (e.g. Cabeza, Nyberg, & Parks, 2005).

Another collection of functional imaging findings provided the basis for the PASA (Posterior–anterior Shift in Ageing) model (Davis, Dennis, Daeslaar, Fleck, & Cabeza, 2008). The PASA model seeks to account for the fact that age-related reductions in occipital cortex activations are often concurrent with increased activation of the frontal cortex. Some of the first authors to document this pattern were Grady et al. (Grady, Maisog, Horwitz et al., 1994) who administered a face and location-matching task to young and older adults. They described how older adults exhibited under-recruitment of occipitotemporal, but over-recruitment of prefrontal areas, relative to young adults. Overactivation in the PFC is a particularly paradoxical observation in the cognitive neuroscience of ageing, since PFC regions are especially susceptible to extensive age-related atrophy of both grey and white matter, and as pointed out above, have been implicated in several age-related cognitive deficits. It has been suggested that older adults draw on more anterior regions to compensate for age-related reductions in the processing efficiency of sensory regions. This PASA pattern

of activation was repeatedly observed across several cognitive tasks, but despite being highly replicable, it was pointed out that the pattern could be construed as age-related differences in task difficulty (Rajah & D'Esposito, 2005). However, when Davies et al. (2008) devised an experiment to investigate this, by controlling for task difficulty across groups, the PASA pattern was still evident. The authors accordingly argued that the PASA pattern reflects intrinsic differences in processing between young and older adults.

Recently, Reuter-Lorenz and Cappell (2008) have synthesised the HAROLD and PASA patterns of activation into one model. They have called this the CRUNCH (Compensation-Related Utilisation of Neural Circuits Hypothesis). This model delineates age-related differences in brain activation and performance as a function of task demands. According to this model, in order to sustain optimal performance in the face of age-related neural declines, older adults need to recruit more cognitive control than young adults, for any given level of task demand. Reuter-Lorenz et al. propose that this recruitment of auxiliary cognitive control, irrespective of task difficulty, is responsible for much of the instances where the PASA pattern has been observed (Cappell, Gmeindl & Reuter-Lorenz, 2011; Reuter-Lorenz & Cappell, 2008). When task demands are increased, older adults may maintain the same level of performance as young adults by recruiting their frontal lobes even more, often increasingly more bilaterally, as reflected in the HAROLD pattern. However, owing to older adults' tendencies to expend more neural resources than young adults at low levels of task demand, they are more likely to reach their resource limitations sooner than young adults, and 'under-recruitment', as well as performance would accordingly ensue (Cappell et al., 2011; Reuter-Lorenz & Cappell, 2008). This model meshes well with the concept of cognitive reserve mentioned above; older adults with higher reserve may reach their resource limit at higher levels of task demand (Stern, 2009), such that over-recruitment is less likely at lower demands.

Interpretations of age-related functional changes

Elucidating the origin and significance of these HAROLD and PASA patterns of functional changes has been a major objective for cognitive ageing research. Two prominent interpretations have been proposed: the *compensatory hypothesis* and the *dedifferentiation hypothesis*. From both points of view, under-recruitment reflects age-related deficits. The effect of over-recruitment, on the other hand, is interpreted differently in each hypothesis. The compensatory hypothesis regards age-related increases in functional activation as a form of compensation that fosters the maintenance of cognitive function. In this view, compensatory over-recruitment could reflect older adults using different brain regions to

implement the same cognitive strategies as young, or using such brain regions to implement different strategies. In contrast, the dedifferentiation hypothesis, which is distinct from the previous discussion of dedifferentiation at the behavioural level, considers that the increased recruitment reflects a generalised spreading of activity due to reduced specificity of brain function (Rajah & D'Esposito, 2005). Here, brief discussions of the evidence supporting each of these interpretations is provided.

One study that is frequently cited as support for the compensation hypothesis was carried out by Cabeza et al. (Cabeza, Anderson, Loantore, & McIntosh, 2002). In this study older adults were divided into two groups of high and low performers based on their performance on four measures of memory. The high performing older adults' performance was indistinguishable from the young control group, whereas the low performing older adults' performance was significantly poorer than both the young control group and the high performing older adults. PET scans revealed that, during a demanding source memory task, young adults and the low performing older adults exhibited predominantly right lateralised anterior PFC activation. In contrast, the high performing older adults showed bilateral anterior PFC activation. This activation pattern was consistent with the HAROLD model and suggested that the more diffuse PFC activation reflected a mechanism geared toward compensating for age-related loss in neuronal efficiency. Several other studies, examining various cognitive domains, have provided support for the compensation approach either by comparing high versus low performing older adults with young adults or by correlating behavioural performance with brain activations (Heuninckx, Wenderoth, & Swinnen, 2008; Rajah & D'Esposito, 2005; Reuter-Lorenz et al., 2000; Reuter-Lorenz, Stanczak, & Miller, 1999; Rypma & D'Esposito, 2000). However, much of this work needs to be interpreted with caution, because, as with all analyses that are correlational in nature, it is not possible to dissociate cause from consequence.

This limitation was highlighted particularly well in a recent study by Schneider-Garces et al. (2010). In this study, fMRI was used to examine brain activity over a range of low- to high-load conditions of a version of Sternberg's memory search task (Sternberg, 1966). It was found that older adults performance did not differ from young adults performance for the low-load conditions, but they performed significantly worse for the high-load conditions. The fMRI data revealed that the older adults exhibited overrecruitment in the low-load conditions and underrecruitment in the high-load conditions. These findings provided strong quantitative support for the CRUNCH model, specifically the idea of the relative recruitment of neural resources depending on task demands. However, the degree to which this pattern was compensation-related was less clear. It was found that the age-related

differences in brain activation could be entirely accounted for by differences in working memory capacity. Specifically, the results suggested that, for any given level of task difficulty, individuals with lower working memory capacities were engaging more diffuse brain regions than those with higher working memory capacities, irrespective of age. The authors point out that, to the extent that compensation constitutes the amount of effort that that is required to achieve a given level of performance, their results are in line with what would be predicted by the compensatory hypothesis. But, the authors also highlight how, owing to the correlational nature of the analyses, it cannot be concluded whether the greater activity was used to improve performance, or whether the lack of some general ability, such as working memory, caused the greater activity and lower behavioural performance.

Some of the most compelling support for the dedifferentiation hypothesis has come from studies that have used repetitive transcranial magnetic stimulation (rTMS) to transiently disrupt neural activity in young and older adults. For instance, in a seminal study conducted by Rossi et al., young and older adults were instructed to study pictures while rTMS was applied to right or left dlPFC. The participants were then required to make recognition judgements while rTMS was again applied to the right or left dlPFC. It was found that for young adults memory retrieval accuracy was compromised more significantly when rTMS was applied to the left than to the right dlPFC. However, for older adults, memory retrieval was affected equally by rTMS, regardless of whether it was applied to the right or left, suggesting an age-related reduction in the specialisation of dlPFC function. Several studies using a variety of other methods have presented similar evidence (Carp et al., 2011; Goh, 2011; Li, 2002; Li, Lindenberger, & Frensch, 2000; Park, Polk, Park et al., 2004; Payer, Marsheuttz, Sutton et al., 2006).

The idea of a dedifferentiation of neural responses with advancing age has also been central to some important neurocomputational models of cognitive ageing. For instance, a model by Li et al. (2000; 2002) proposes that age-related deficits in the dopaminergic system shape the functional organisation of neural and cognitive processes. More specifically, they advance that age-related declines in dopamine levels compromise neuronal signal transmission, which leads to a reduction in signal to noise ratio, and that this increase in neural noise in turn leads to less distinctive neurocognitive representations. They used neural network simulations to test whether this model could recapitulate several benchmark behavioural phenomena in cognitive ageing research. They found that age-related differences in interference susceptibility, intra- and inter-individual variability, dedifferentiation of cognitive and sensory abilities, as well as many other recurrent observations, could all be successfully modelled. These findings thus implicate age-related dysfunction of the

dopaminergic system as an important mediator of cognitive ageing in general, but also specifically in the dedifferentiation that has been observed at both the behavioural and neural level in older adults.

Thus, comparable quantities of evidence seem to have accumulated in support of both the compensatory and dedifferentiation hypotheses. More recently, an integrative theory known as *The Scaffolding Theory of Cognitive Ageing*, has proposed an account for age-related cognitive decline that allows for the compensatory and dedifferentiation hypotheses to be considered in a complementary way (Goh & Park, 2009; Park & Reuter-Lorenz. 2009; Reuter-Lorenz & Park, 2010).

The scaffolding framework was originally proposed to describe the recurrent observation of how during novel tasks, high-level brain regions other than task-specific brain regions, are often recruited to serve as a scaffold for the yet inefficient task specific regions (Petersen, van Mier, Fiez & Park, 1998). These scaffolding regions typically include areas such as the PFC, anterior cingulate cortex (ACC), and posterior parietal cortex, which are associated with attention and cognitive control (Kelly & Garavan, 2005; Kelly, Foxe, & Garavan, 2006). These regions are relied on to cope with novel task demands. According to the scaffolding theory of ageing, in the face of age-related neural declines and less efficient neural networks, the ageing brain recruits auxiliary neural networks to reinforce damaged structures and preserve levels of cognitive functioning. Most frequently, this entails PFC regions compensating (compensatory hypothesis) for the decreased specificity (dedifferentiation hypothesis) of posterior regions (Goh & Park, 2009). The consistent implication of the PFC in this regard has been attributed to both its role in attentional control and its status as the most flexible structure in the brain (Park & Reuter-Lorenz, 2009).

Empirical support for the co-occurrence of compensation and dedifferentiation has been provided in a study by Carp, Gmeindl & Reuter-Lorenz (2010). Using fMRI, they carried out a multi-voxel pattern analysis of the distinctiveness of neural representations in young and older adults. Consistent with the dedifferentiation hypothesis, they observed a reduction in the distinctiveness of visual cortical representations in older adults. However, at odds with the dedifferentiation hypothesis, at levels of low task demand, older adults had more distinct PFC activation compared to young adults. These findings were interpreted as the PFC demonstrating compensatory activity for the less distinctive representations in the visual cortex. For high task demands the pattern reversed, however, and became less distinctive in older adults and more distinctive in young adults. The older adults presumably reached the upper limit of their capacity to compensate, whereas young adults had recruited additional support to maintain performance. Carp et al. concluded that comprehensive

theories of cognitive ageing should incorporate tenets of both the compensatory and the dedifferentiation hypotheses.

However, it should be noted that the same authors failed to reproduce these findings in a subsequent investigation (Carp et al., 2011), where instead, the findings appeared to support the dedifferentiation hypothesis and challenge the compensatory hypothesis. Further, in one of the first studies of age-related functional changes with a longitudinal design, Nyberg et al. found that although frontal lobe over-recruitment was apparent in initial cross-sectional sectional analyses, when the same cohort was followed up 6 years later there was a reduction in frontal lobe recruitment. This reduction was particularly prominent in the right dlPFC (Nyberg, Salami, Andersson et al., 2010). Thus, this finding also challenges the notion of age-related reorganisation of the brain for functional compensation, and instead points to a more direct relationship between age-related declines in frontal structure and declines in frontal functional response.

Summary

Structural and functional neuroimaging techniques have provided valuable, non-invasive, methods for gaining insight into how the ageing process affects neural structure and function. Three general phenomena have been observed particularly consistently: 1) an anterior-to-posterior gradient of structural degeneration; 2) HAROLD reflecting a reduced lateralisation of processing across the hemispheres; and 3) PASA, reflecting a shift in functional activity from posterior sensory regions to more anterior high level cognitive regions. Although the patterns of age-related cognitive, structural and functional changes are all relatively well characterised, relating the changes in cognitive performance to the age-related structural and functional changes has proven challenging. The origin and significance of the HAROLD and PASA patterns continue to be matters of considerable debate. Indeed there is increasingly more consensus that the ageing process is associated with more variability across neural systems and across individuals than is typically accounted for in most neurobiological theories of ageing (Andrews-Hanna, Snyder, Vincent et al., 2007; Buckner, 2004). In the context of this thesis, the extensive declines in the structure and function of the frontal lobe is of particular relevance, because as will be demonstrated, in the next section, metacognitive abilities appear to be predominantly reliant on frontal lobe structures.

1.3 Metacognition

As we have seen from the previous section, the ageing process does not affect all brain functions or structures in the same way. A major aim of this thesis is to determine whether metacognitive capacities are compromised in older adults. Metacognition, or 'cognition about cognition,' refers to the diverse processes of self-monitoring, self-knowledge and self-regulation that contribute to the adaptive control of cognition and behaviour (Cicerone & Tupper, 1996; Mazzoni & Nelson, 1998; Metcalfe & Shimamura, 1996). Given the far-reaching importance of metacognition, as well as its heterogeneous nature, it is not surprising that metacognition has been a topic of research interest in several different disciplines. However, the organising idea in this area of enquiry is that humans have a domain, or domains, of information processing that comprise personal awareness and knowledge, as well as adaptive strategies that monitor and control cognitive processes.

This section constitutes a discussion of metacognition and self-awareness in their broadest sense, as they relate to clinical research. Section 1.3 then provides a more focussed review of a specific field of enquiry that falls within the rubric of 'self-awareness,' but is specifically concerned with the online detection of performance errors. It is argued that this field may provide fundamental insights regarding the core neural mechanisms that form the foundations of metacognitive abilities.

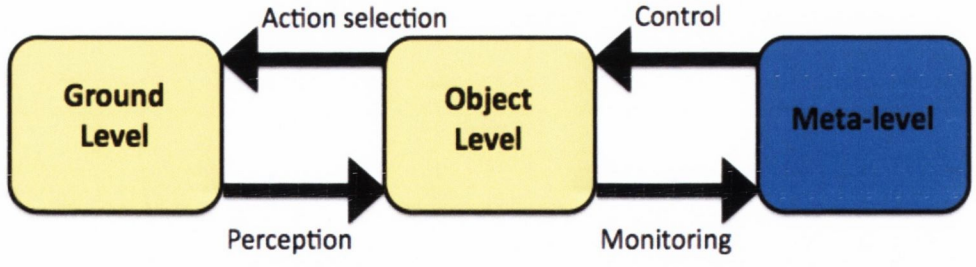

Figure 1.1 Schematic of metacognitive monitoring and control of cognition.
Figure adapted from Nelson and Narens (1990).

Nelson and Narens (1990) proposed a psychological framework that serves as a useful heuristic for understanding metacognition. In this framework, illustrated in **Figure 1.1**, they made a dissociation between an 'object level' (cognition) and a 'meta-level' (metacognition), such that the meta-level holds a dynamic model of the object level. The links between the ground level and object level represent a classic action and perception

cycle. Phenomena at the ground level are perceived through an assemblage of sensors. In response, a sequence of actions is selected at the object level and executed through the individual's effectors. This interacts with, and alters, the environment at the ground level, and the cycle continues. Metacognition is essentially cognition about this action-perception cycle. The flow of information from the object level to meta-level is considered *monitoring*, whereas the flow of information from the meta-level to the object-level is considered *control. Monitoring* informs the meta-level about the state of the object-level, and accordingly allows the meta-level's model of the object-level to be dynamically updated. Subsequently, depending on the discrepancy between intended and actual performance, *control* can maintain, adapt or terminate object-level processes (Nelson, Narens, Metcalf, & Shimamura, 1994). Thus, monitoring ongoing performance permits evaluation of whether more cognitive effort is necessary to achieve current goals. It can also impart a sense of confidence or uncertainty that can optimise performance in several contexts. For example, in multiple choice exams the opportunity to 'opt-out' of a decision is often provided; if there is a penalty for incorrect answers, then knowing you do not know is highly advantageous (Higham, Perfect & Bruno, 2009). Similarly, monitoring ongoing performance facilitates appraisal of personal abilities, and predictions about subsequent performances (e.g. Dobbs & Reevs, 1996). For instance, the inspiration to create external memory aids (e.g. shopping lists) ensues from an expectation that, on the basis of past experience, items are likely to be forgotten otherwise. By extension, if the meta-level's monitoring of the object level is compromised, self-knowledge about cognition will be inaccurate. This would conceivably manifest as a lack of awareness of performance.

While accurate self-monitoring and awareness of one's abilities is essential for adaptive functioning throughout life, the need for it is arguably increased in late life when deterioration of cognitive functions, of at least some degree, invariably occurs. Yet, the extent to which these capacities are affected by the natural ageing process is largely unknown. This section begins with an overview of the literature on the clinical phenomenon, ansosognosia. Although a comprehensive understanding of this phenomenon is still lacking, the literature on anosognosia provides important information on the multidimensionality of metacognitive abilities, how they can be measured and what is currently known about their neuropsychological and neuroanatomical bases.

1.3.1 Anosognosia

A rich literature documents how patients with neurological conditions, particularly those with damage to right frontal regions, often present with a reduced capacity to reflect upon their cognitive capacities and functional limitations, a phenomenon termed anosognosia (Babinski, 1914; McGlynn & Schacter, 1989). Anosognosia has also been used interchangeably with impaired self-awareness. Although self-awareness (SA) can have several different connotations, in the context of this literature, and this thesis, it is defined as the accuracy with which individuals can appraise aspects of their cognitive and behavioural functioning (Roberts, Clare, & Woods, 2009). Patients with anosognosia will often insist they have no significant problems, despite experiencing significant functional impairment in work and daily living owing to a deterioration in cognitive and socio-emotional abilities. Given that self-appraisals guide much of human behaviour, it is not surprising that anosognosia can yield significant deleterious consequences, including distress in families and care-givers (Clare, Whitaker, Nelis et al., 2011; Seltzer, Vasterling, Yoder, & Thompson, 1997), and safety risks for patients and those around them (Cotrell & Wild, 1999; Starkstein, Jorge, Mizrahi, Adrian, & Robinson, 2007). The level of SA maintained by these patients has also been known to have implications for general prognosis, perceived quality of life, vocational potential, and return to independent living (David, 1992; Evans, Sherer, Nick, Nakase-Richardson, & Yablon, 2005; Flashman & McAllister, 2002; Godfrey, Partridge, Knight, & Bishara, 1993; Kervick & Kaemingk, 2005; Ownsworth & Fleming, 2005; Prigatano, 1997; Seltzer, Vasterling, Yoder, & Thompson, 1997; Sherer et al., 2003; Tabert, Albert, Borukhova-Milov et al., 2002; Trahan, Pépin, & Hopps, 2006). Furthermore, impaired SA may delay medical consultation regarding incipient dementia and can affect compliance to treatment and rehabilitation efforts (Fleming, Strong, & Ashton, 1996; Griffith, Dymek, Atchison, Harrell, & Marson, 2005; Koltai, Welsh-Bohmer, & Schmechel, 2001; Patel & Prince, 2001). The prevalence of anosognosia in Alzheimer's Disease (AD) has been estimated to be as high as 80% (Agnew & Morris), and although the non-AD dementias have been studied comparatively less (O'Keeffe, Murray, Coen et al., 2007), according to Neary et al. anosognosia occurs so early and frequently in frontotemporal dementia (FTD) that it is a principal criterion for diagnosis (Neary, Snowden, Gustafson et al., 1998). Tabert et al. (2002) have also documented that impaired awareness of cognitive deficits in mild cognitive impairment, often a precursor to AD, has been linked to an increased likelihood of advancement to dementia. Despite the prevalence and impact of anosognosia on patients with neurological conditions and their caregivers, the phenomenon remains poorly understood. Several explanations of anosognosia have been put forward over the years, including ones that attribute it to a severe impairment in learning new information

(Sunderland, Harris, Baddeley, 1993) or a psychological defence against the realisation that one is suffering from irreversible cognitive decline (Reisberg, Gordan, McCarthy & Ferris, 1985; Sevush & Leve, 1993; Weinstein, 1991). More recently, growing evidence implicates the cognitive and neural networks that are critical for processes of self-evaluation (Johnson, Baxter, Wilder et al., 2002; Johnson, Ries, Hess et al., 2007; Zamboni, Drazich, McCulloch et al., 2013), but as will be outlined below, the precise mechanisms through which these networks enable self-awareness remains unclear.

Measuring Self-awareness

Many approaches to measuring SA have been employed in the literature, but most can be broadly described as involving the elicitation of judgements about cognitive abilities and deficits as they might apply to various activities in everyday life (e.g., "Do you find you forget appointments? Broadbent, Cooper, Fitzgerald & Parkes, 1982). As such these measures are assumed to tap into long-term memory representations, or 'metacognitive knowledge' (Toglia & Kirk, 2000), about one's personal abilities (Fleming, Strong & Ashton, 1996; Mograbi, Brown & Morris, 2009). A number of studies have also measured metacognitive abilities using online assessments, which involve examining an individual's monitoring and evaluation of their performance while they are engaged in a specific task (Hertzog & Dunlosky, 2011; Prigatano & Schacter, 1991). However, to date, the extent to which performance on such online assessments is associated with the phenomena captured by the former approach is largely unknown.

The most common approach to measuring SA in clinical populations, is to compare self-reports on questionnaire measures of daily functioning with those of a close informant, with the premise that a discrepancy in the direction of the informant reporting more difficulties indicates an impairment in SA (Fleming, Strong & Ashton, 1996; Hart et al., 2004). A major caveat of this approach is that it is time and labour-intensive, requiring the administration of two questionnaires and the presence of the informant. This approach also assumes that the informant provides objective ratings, but the informant ratings are difficult to validate, and could be susceptible to several different biases in either the direction of under-reporting (e.g. because they do not want to demean the person they care for) or over-reporting (e.g. stereotypes) difficulties (Bach & David, 2006; Bogod, Mateer & MacDonald, 2003; Clare et al., 2004; Fleming, 1986). Nonetheless, studies using these types of collateral ratings to study anosognosia have provided valuable data on the phenomenon. This method has revealed that traumatic brain injury (TBI) and AD patients, among other clinical populations, consistently rate themselves as less impaired than their informants (e.g.

DeBettignies, Mahurin & Pirozzolo, 1990; Mangone, Hier, Gorelick et al., 1991; McGlynn & Kaszniak, 1991; Sherer et al., 1998). Moreover, informant ratings of patient abilities have been found to correlate significantly with objective performance on tests (Feher, Mahurin, Inbody, Crook & Pirozzolo, 1990), whereas patients' self-ratings were unrelated to the test scores (Feher et al., 1990; Robertson, Manly, Andrade, Baddeley & Yiend, 1997). In addition, greater discrepancy scores have been associated with poorer performance on activities of daily living (Salmon et al., 2006), and poorer employment outcome (Sherer et al., 1998).

While these findings seem to support the validity of the collateral rating method for measuring metacognition, there is no consistency or consensus in the literature regarding the best questionnaire(s) to use. It is clear that SA is not a unitary construct; rather it varies across functional domains. For instance, studies have documented striking dissociations between the accuracy with which various clinical populations appraise some domains of functioning relative to others. For instance, TBI patients are characteristically more aware of physical deficits and difficulties performing activities of daily living (ADLS), than they are of cognitive, behavioural or social sequelae (Bivona et al., 2008; Hart, Sherer, Whyte et al., 2004; Prigatano & Altman, 1990; Sherer et al., 2003; Teasdale, Christensen, Willmes et al., 1997). Patients with Parkinson's disease (PD) often show relatively intact awareness of their cognitive deficits, but have poor awareness of self-care and social deficits (Leritz, Loftis, Crucian, Friedman & Bowers, 2004; Seltzer, Vasterling, Mathias & Brennan, 2001). AD patients also frequently demonstrate considerable variability in their awareness across different domains of cognition and behaviour (e.g. Green, Goldstein, Sirockman, & Green, 1993; Wild & Cotrell, 2003). The choice of questionnaire should thus be guided by the specific domain or 'object' under question (Fleming et al., 1996; Markova & Berrios 2011), and multifaceted assessments of SA should be employed more routinely.

The second most common approach to assessing SA is to obtain ratings of awareness through interviews conducted by a clinician or researcher. Ratings are typically based on of a combination of estimating levels of awareness based on the patient's history and neuropsychological testing (Ott, Lafleche, Whelihan et al., 1996; Verhey, Rozendaal, Ponds & Jolles, 1995; Zanetti, Vallotti, Frisoni et al., 1999). This approach does seem to yield similar patterns of findings to collateral-rating based methods, but considering much of what the clinician or researcher knows about a patients day-to-day functioning and history is based on information provided by the informant, the distinction between the two approaches is not clear.

Online approaches have been employed far less frequently but typically involve calculating discrepancies between patients' predictions or post-dictions of performance, and actual task performance (Barrent, Eslinger, Ballentine et al., 2005; Eslinger, Dennis, Moore et al., 2005; Wagner, Spangenberg, Bachman & O'Connell, 1997). This approach is appealing because it does not require a separate informant, but it has its limitations. The most significant of these concerns subjectivity and ecological validity. Due to the fact that neuropsychological assessments are typically designed to probe specific cognitive domains as opposed to more functional abilities, it may be difficult for even the most cognitively intact individuals to make accurate estimations of their performance. A slight variant of this approach, utilising computerised paradigms, has been employed less frequently, but appears to show promise. This has involved subjects overtly signaling their errors during neuropsychological tasks. Errors are typically signaled by pressing a button which is not used for the primary task, and SA is accordingly operationalised as the ratio of signaled errors to total errors. A number of studies using these types of error signalling measures have found that individuals with TBI (Hart, Giovannetti, Montgomery & Schwartz, 1998; McAvinue, O'Keeffe, McMackin, & Robertson, 2005), attention-deficit hyperactive disorder (ADHD; O'Connell et al., 2009), psychopathy (Brazil et al., 2009), FTD (O'Keeffe, Murray, Coen et al., 2007) and drug addiction (Hester et al., 2009) demonstrate compromised awareness of their errors relative to healthy controls. An important advantage of this approach is that it is completely objective, but again, the extent to which deficits on these tasks relate to awareness of real-world cognitive functioning is not yet clear.

Neuropsychological Correlates of Self-awareness

There seems to be reasonable consensus across studies investigating the neuropsychological correlates of anosognosia in clinical populations that anosognosia cannot be explained by the severity of cognitive impairment alone (e.g. Hannesdottir & Morris, 2007; Reed et al., 1993; Vocat, Saj & Vuilleumier, 2013). There is less agreement surrounding the extent to which anosognosia may be related to more specific domains of functioning. Memory and executive functioning have been implicated most consistently as neuropsychological correlates of SA. Here, the literature that has examined these relationships is discussed.

Common sense would dictate that a patient could not become aware that their capacities are compromised if they forgot about incidents where they did not succeed to fulfill a goal. One proposed mechanism for impaired SA is that memory deficits result in a failure to update self-relevant knowledge due to memory deficits, leading to an outdated

sense of self. This has become known as the "Petrified Self" hypothesis (see Mograbi, Brown & Morris, 2009), and has been supported by a number of studies that have found significant relationships between memory scores and the accuracy with which patients appraise their abilities (Feher et al., 1991; Gallo, Chen, Wiseman, et al., 2007; Mangone et al., 1991; Migliorelli et al., 1995; Noe, Ferri, Cabballero et al., 2005; Souchay, Isingrini et al., 2002; Trudel, Tyron, & Purdum, 1998). However, several other studies have not shown such a relationship (Auchus, Goldstein, Green, & Green, 1994; Derouesne et al., 1999 Lopez, Becker, Somsak, Dew, & DeKowsky, 1994; Reed et al., 1993; Vogel, Hasselbalch, Gade, Ziebell, & Waldemar, 2005; Zamboni, Grafman, Krueger et al., 2010). Some of the variability across these studies could be related to the nature of the particular memory test that is employed. For instance, Gallo et al. (2007) have provided evidence to suggest that measures of SA and memory are more likely to correlate, when memory tests require the effortful retrieval of nondistinctive information.

Several studies have contradicted the memory-based explanation by showing that impairments in SA correlate with neuropsychological measures sensitive to executive functioning, even after co-varying for memory abilities (e.g. Lopez et al., 1994; Michon et al., 1994; Migliorelli et al., 1995). As previously described, executive functioning is a term that captures a collection of higher order cognitive processes that are responsible for complex behaviours such as monitoring, sequencing, problem-solving, focussing attention and initiation of action (Pennington & Ozonoff, 1996). Norman and Shallice (1986) have proposed a model called the "Supervisory Attentional System" wherein executive functioning serves a supervisory role, monitoring and manipulating more basic processes. As such, this model bears a marked similarity to the previously described model of metacognition proposed by Nelson and Narens (1990). Both models incorporate higher order levels that monitor and control more basic information processing. This correspondence between executive functioning and metacognition to act as regulatory systems has prompted several authors to advance that the two processes may be related (e.g. Fernandez-Duque, Baird, & Posner, 2000; Hart, Whyte, Kim & Vaccaro, 2005; Michon, Deweer, Pillon, Agid, & Dubois, 1994; Shimamura, 2000). Several studies have indeed found a correlation between executive functioning and metacognitive abilities in a range of clinical populations (e.g. Bogod, Mateer, Stuart & MacDonald, 2003; Lopez, Becker, Somsak, Dew, & DeKosky 1994; Dalla Barba, Parlato, Iavarone, & Boller 1995; Souchay, Isingrini, Clarys, Tacconat, & Eustache, 2004). The putative relationship between these two processes is further supported by a host of neuroimaging studies demonstrating that executive functioning (e.g. Chen,Wei, & Zhou, 2006; Collette, Hogge, Salmon, & Van Der Linden, 2006; Markela-Larenc, 2004; Stuss & Alexander, 2000) and metacognitive abilities (e.g. Chua, Schacter, Rand-

Giovannetti, & Sperling, 2006; Chua, Schacter, & Sperling, 2009; De Martino, Fleming, Garret, & Dolan 2013; Fleming, Huijgen, & Dolan, 2012; Fleming, Weil, Nagy, Dolan & Reis, 2010; Kikyo, Ohki, & Miyashita, 2002) are both strongly reliant on the frontal lobes.

These associations have prompted various hypotheses regarding which capacity contributes to the other. One perspective asserts that the attentional control afforded by executive functions is required for metacognitive processes such as self-monitoring and self-reflection (Hart et al., 2005). An alternative hypothesis is that metacognitive judgements themselves are critical for the exertion of executive control over behaviours. Consistent with this latter hypothesis, Metcalfe (2009), among others (Karpicke, 2009; Redford, 2010), has reported that adjustments in behaviour are linked to judgements about performance in healthy individuals. However, overall, the findings regarding the relationship between SA and executive functions are quite mixed (Bach & David, 2006; Bivona et al., 2008; Sherman, Rapport & Ryan, 2008; Stuss & Levine, 2002; Suchy, Kraybill & Franchow, 2011).

These inconsistent findings may be attributable, at least in part, to the broad range of skills covered under the rubric of executive functioning (Hart et al., 2005) and the fact that there is no comprehensive assessment of executive functioning (Bivona et al., 2008). As a consequence many tests that are advanced as measures of executive function typically only analyse discrete aspects (e.g. response inhibition or planning). One arguable exception is the WCST, which has been endorsed as a measure of multiple components of executive functioning, including response inhibition, set-shifting, abstract reasoning, problem solving, cognitive flexibility, and hypothesis generation (Hanks et al., 1999; Mukhopadhyay et al., 2008). Still, studies of SA that have used the WCST as an index of executive functioning have failed to produce a consistent pattern of results. Friedman et al. have recently highlighted that aside from drawing upon the mentioned executive functions, the WCST also places considerable demands on perceptual, motor, and other cognitive abilities, and that this task impurity makes it unclear to what extent both null and positive results reflect such nonexecutive variance (Friedman et al., 2009).

There is some basis for speculating that specific components of executive functioning should have closer relationships with SA than others. For instance, sustained, or vigilant, attention requires attention over time to both the task itself, and to one's state of attentiveness to the task, the latter of which requires self-monitoring (Robertson, 2010). Robertson (2010) has proposed a model wherein accurate metacognitive knowledge is contingent on paying sufficient attention to moment-to-moment performance. Inherent to this model is that errors in performance are a key source of information about one's personal abilities, and the stipulation that these errors will only reach the threshold for conscious

access if the individual is sufficiently vigilant of their moment–to-moment performance. Other authors have similarly argued that lapses of attention would disrupt the continuity of conscious experience, and may accordingly preclude awareness of functional failures as they occur in everyday life (Frith, 1992; Hart, Giovannetti, Montgomery & Schwartz, 1998). In accord with this, several studies have indeed found a strong relationship between sustained attention ability and SA as indexed by discrepancy scores using the collateral rating method, as well as measures of online error awareness (Hart et al., 1998; Hoerold et al., 2008; O'Connell et al., 2009; O'Keefe et al., 2007; McAvinue et al. 2005; Shalgi et al., 2007). In light of this, the view taken in this thesis is that investigating older adults' capacities for performance monitoring and error awareness, and their relationship with SA as measured using the collateral rating approach, may be fruitful for understanding the extent to which metacognitive abilities are affected by the natural ageing process.

Neural Correlates of Self-awareness

The memory-based explanation for anosognosia has also been challenged at the neuroanatomical level. For instance, it has been found that many patients with TBI (Levin, Benton, Grossman et al., 1982; Sunderland, Harris et al., 1983; Sunderland, Harris et al., 1984), anterior communicating artery aneurysms (Alexander & Freedman, 1984; Vilkki, 1985; Volpe & Hirst, 1983), and amnesia from Korsakoff's syndrome (Talland, 1965; Victor, Adams et al., 1971; Zangwill, 1966) demonstrate partial or no awareness of their memory problems, and this awareness deficit has been associated with compromised functioning of the frontal cortex rather than medial temporal lobe. Yet, although the frontal cortex has been consistently implicated, areas within the parietal, temporal and insular cortices, as well as a number of sub-cortical structures have also frequently been identified as correlates of anosognosia (Cooke, Fannon, Kuipers al., 2008; De Witte, Brouns, Kavadias et al., 2011; Pia, Neppi-Modona, Ricci, Berti et al. 2004; Prigatano & Schacter, 1991; Rosen et al., 2010). Indeed, given the multidimensional nature of anosognosia, it is likely to result from combinations of several deficits affecting different domains, with corresponding multifocal neural correlates. Nevertheless some brain regions have been highlighted more consistently than others. The following subsection proceeds with an evaluation of the literature relating to two structures that have been implicated particularly consistently: the right frontal lobe and the anterior insular cortex.

The brain region that has been implicated the most consistently in the neuroanatomy of anosognosia, irrespective of the clinical population under question, is the right frontal lobe. Studies have repeatedly demonstrated a strong association between anosognosia and

hypoperfusion and hypometabolism of right dlPFC in neurodegenerative diseases such as AD and FTD (Antoine et al., 2004; Harwood et al., 2005; Mendez & Shapira, 2005; Mimura & Yano, 2006; Reed, Jagust et al., 1993; Salmon, Perani et al., 2006; Sedaghat, Dedouisi, Baloyannis et al., 2010; Shany-Ur, Lin, Rosen et al., 2014; Starkstein et al., 1995). Similarly, awareness of impairment in schizophrenia patients has been associated with right (see **Figure 1.2**), but not left, dlPFC volume (Shad, Muddasani, Prasad, Sweeney, & Keshaven, 2004; Shad, Muddasani, & Keshaven, 2006; Spalletta, Piras, Piras, Caltagirone, & Orfei, 2014).

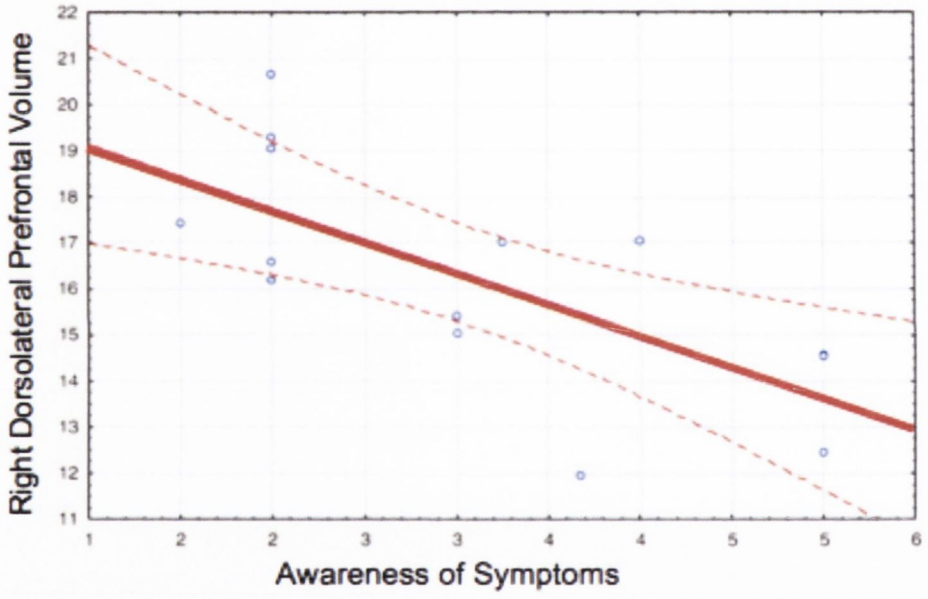

Figure 1.2. Relationship between right dorsolateral prefrontal cortex volume and awareness of symptoms. Scatterplot of average scores on current awareness of symptoms with right dorsolateral prefrontal cortex volume in patients with schizophrenia. Spearman's $R = -0.72$; $P = 0.003$ (Shad et al., 2004).

While lateral regions of the right frontal lobe seem to be implicated most frequently, many studies have also highlighted more medial regions (Ries, Jabber, Schmitz et al., 2007; Ries, McLaren, Bendlin et al., 2011; Rosen, Alcantar, Rothlind et al., 2010; Zamboni et al., 2013). For instance, using voxel-based morphometry, Rosen et al. found that in a sample of individuals with diverse neurodegenerative diseases, greater overestimation of cognitive

performance was uniquely associated with reduced grey matter volume in right ventromedial PFC (Rosen et al., 2010). Much work has also linked anosognosia for hemiplegia with right fronto-parietal dysfunction (for reviews see Pia, Neppi-Modona, Ricci, & Berti, 2004; Orfei, Robinson, Prigatano et al., 2007). These findings are additionally consistent with a comparatively earlier brain lesion literature documenting a reliable association between right hemisphere lesions and anosognosia in a range of clinical conditions (Battersby, Bender et al., 1956; Bisiach, Vallar et al.,1986; Bisiach & Geminiani, 1991; Cobb, 1947; Goldberg & Barr, 1991; McGlynn & Schacter, 1989; Von Hagen & Ives, 1937; Waldenstrom, 1939; Warrington, 1962).

Outside of the clinical literature, researchers are also beginning to highlight the importance of the right frontal lobe in mediating metacognitive abilities in healthy young adults. For instance, tasks that require self-referential appraisal have been associated with a preferential right dlPFC neural response relative to those that do not require appraisal of oneself (e.g. Fossati, Hevenor, Graham et al., 2003; Schmitz, Kawahara-Baccus & Johnson, 2004). Further, an interesting series of studies have recently provided structural and functional evidence that point to a specific role of right lateral prefrontal regions in mediating the capacity for subjective assessment of decision confidence (De Martino et al., 2013; Fleming et al., 2010; 2012; Yokoyama, Miura, Takemoto et al., 2010). Finally, transcranial magenetic stimulation (TMS) administered over dlPFC has been found to disrupt metacognitive abilities in healthy young adults (Rounis, Maniscalco, Rothwell, Passingham, & Lau, 2010), although, no conclusions about a privileged role of right frontal regions could be derived in this particular study, as stimulation was delivered bilaterally.

Several studies have also emphasised the role of the insular cortex in anosognosia (Baier & Karnath, 2008; Berti, Bottini, Gandola et al., 2005; Goldstein, Craig, Bechara et al., 2010; Karnath, Baier & Nagele, 2005; Palaniyappen, Mallikarjun, Joseph & Liddle, 2011; Orfei et al., 2007; Shany-Ur et al., 2014; Spalletta et al., 2014; Spinazzola, Pia, Folegatti, Marchetti & Berti, 2008; Vocat, Staub, Stroppini & Vuilleumier, 2010). As with the frontal lobe, studies have implicated right more than left lateralised areas of the insular cortex. For instance, using high resolution magnetic resonance imaging (MRI), Palaniyappan et al. (2011) found a significant relationship between the integrity of the right posterior insula and degree of SA in schizophrenia patients. No such relationship was observed for left posterior insula. Lesions of the right insula have also been associated with anosognosia for hemiplegia and hemianesthesia (Karnath et al., 2005; Spiazzola et al., 2008). Furthermore, in a very recent study of patients with neurodegenerative diseases, Shany-Ur et al. (2014) used voxel-based morphemetry to examine the neural correlates of SA across four functional domains,

which included daily living activities, cognitive abilities, emotional control, and interpersonal functioning. They found that most patients overestimated their functioning across all four functional domains, relative to how their informants rated them; and a composite score for SA of one's overall functioning was significantly associated with atrophy in a network that included right greater than left frontal and subcortical regions. However, when they analysed specific domains of function separately, distinct neuroanatomical patterns emerged. No single region was implicated across all four domains, but the degree of atrophy in the right anterior insula correlated with overestimation of competence across three of the four domains: activities of daily living, emotional control and interpersonal abilities. Outside of the literature on anosognosia, the insular cortex is broadly accepted as a critical substrate for supporting interoceptive awareness (Craig, 2009; Critchley, Wiens, Rotshein et al., 2004; Seth, Suzuki, & Critchley, 2011; Simmons, Fitzpatrick, Strigo et al., 2012). The anterior insula, in particular, has also been implicated in online performance monitoring processes such as implicit and explicit error detection, as well as decision making under uncertainty (Harris, Sheth, & Cohen, 2008; Pourtois, Vocat, N'Diaye et al., 2010; Singer, Critchley, & Preeuschoff, 2009; Ullsperger, Harsay, Wessell, & Ridderinkhof, 2010), which may have an important role in promoting awareness of deficits (Robertson, 2010; Vocat & Vuilleumier, 2010).

1.3.2 Metacognitive abilities in healthy older adults

As already mentioned, although metacognitive knowledge has been a topic of much scrutiny in several clinical populations, markedly little is known about how metacognitive abilities might be affected by the natural ageing process. One area that has been the subject of a modest amount of research is awareness of memory functioning, often termed metamemory (Bieman-Copland & Charness, 1994; Bruce, Andrew, & Botwinick, 1982; Clare, Whitaker & Nelis 2010; Graham, Kunik, Doody & Snow, 2005; Kelley & Sahakyan, 2003; Perrotin, Isingrini, Souchay, Clarys, & Tacconat, 2006; Ries, McLaren, Bendlin et al., 2012; Souchay & Isingrini, 2004; Souchay, Insingrini & Espagnet, 2000). Some studies have employed what is known as the feeling-of-knowing (FOK) paradigm to investigate memory monitoring and its accuracy in healthy older adults relative to young adults. The FOK paradigm is essentially a variant of the online approaches discussed above, wherein participants are required to make a judgement about the likelihood that they will remember particular items prior to performing a recognition task. The accuracy of FOK judgements are typically determined using the Goodman-Kruskal gamma correlation (Goodman & Kruskal, 1959). The gamma correlation is an index of relative accuracy that ranges between -1 and

+1, and indicates to what extent items that are judged as relatively more difficult are remembered less on the recognition task, and vice versa. Accordingly, the greater the gamma correlation, the closer the judgement of performance is to actual performance on the recognition task. Studies have found that the gamma correlation is weaker for older relative to young adults (Perrotin, Isingrini, Souchay, Clarys, & Tacconat, 2006; Souchay & Isingrini, 2004; Souchay, Insingrini & Espagnet, 2000), suggesting that the accuracy with which individuals can appraise their memory abilities may decline with age. Further, it was found that executive functioning mediated age-related differences in FOK judgments in two of the studies (Perrotin et al., 2006; Souchay et al., 2000), and speed of processing mediated age-related changes in recall in the study by Perrotin et al. (2006).

Bieman-Copland and Charness (1994) also examined differences in memory monitoring between young and older adults. Their study entailed two separate trials where participants made predictions about their performance on word recall tasks with three types of experimental cues (rhyme, letter and meaning). There were no group differences in the predictions for either of the trials for any of the cue types. However, the accuracy of predictions varied both as a function of group and cue type. Older adults overestimated their performance with rhyme and letter cues, but accurately predicted their performance with meaning cues. While younger adults also overestimated their performance with rhyme cues, they accurately predicted their performance with letter cues, and underestimated their performance with meaning cues. On the second trial, older adults significantly decreased their predictions for all three cue types, but there was still a significant discrepancy between their predictions and actual performance for rhyme and letter cued word recall. In contrast, young adults demonstrated improved accuracy in their predictions of performance for all three cue types, reducing their prediction for rhyme cued recall, and increasing their prediction for meaning cued recall. These findings suggest that older adults were able to update their awareness of their memory capacity based on experience to a certain extent, but they were not able to do so as efficiently as young adults. Speed of processing also accounted for some but not all of the memory-monitoring differences in this study. At least three other studies have found that when young and older adults were asked to make confidence judgements or predictions about their performance on a memory task, older adults significantly overestimated their memory, relative to both objective task performance, and relative to young adults (Bruce, Andrew, & Botwinick, 1982; Graham, Kunik, Doody & Snow, 2005; Kelley & Sahakyan, 2003).

Conversely, Clare, Whitaker and Nelis (2010) have suggested that awareness of memory function is not vulnerable to the effects of the natural ageing process. They

employed the collateral rating approach to compare awareness of memory functioning in AD patients with healthy older adults and found that healthy older adults had better awareness of their memory functioning relative to AD patients, and as an independent group, healthy older adults' self-ratings were in close agreement with those provided by their informant (i.e. discrepancy scores were close to zero). Ries et al. (Ries, McLaren, Bendlin et al., 2012) have since replicated this finding in a smaller sample.

Outside of the memory domain, Rabbitt (1990; 2002) has carried out two studies where he compared young and healthy older adults' online error awareness, as indexed by their ability to signal their errors during a simple serial choice reaction time task. These two studies will be discussed in more detail below (see *Error awareness in healthy ageing*, this chapter), but in short, the results of the first study suggested that older adults demonstrated diminished awareness of their performance errors (Rabbit, 1990); whereas, the results of the second study suggested that the capacity for error awareness is preserved in non-pathological ageing, but that older adults simply require more time to consciously recognise their errors than young adults (Rabbit, 2002). Another study by Ross and colleagues recently examined older adults awareness of their driving competency (Ross, Dodson, Edwards, Ackerman, & Ball, 2012). They found that when older adults, aged between 65 and 91 years, were asked to rate their driving abilities, most (85%) of the older adults in this range rated themselves as 'excellent' or 'good' drivers, irrespective of actual driving proficiency as indexed by previous crash involvement or being pulled over by the police. The lack of a young control group in this study limits the conclusions that can be drawn regarding age-related changes, but the findings nonetheless suggest older adults' self-appraisals of driving competency are not likely reliable indicators of actual driving competency. Two further studies have examined discrepancies between older adults self-reports and objective performance of activities of daily living (ADL; Suchy, Kraybill & Franchow, 2011; Souchay, Isingrini, Clarys & Taconnat, 2004). While the lack of young control groups in these studies again made it impossible to infer any age-related changes, both studies documented considerable inter-individual variability in levels of self-awareness in the samples. Suchy et al. (2011) suggested that relatively poor awareness in otherwise healthy older adults might be mediated by lower cognitive reserve.

Summary

Metacognition is a broad construct, representing diverse high-level processes involved in the monitoring and evaluation of cognitive processes. The study of anosognosia, a common sequela of many neurological conditions, has provided important information on

the possible neuroanatomical substrates that support metacognition, and its relationship to other aspects of cognitive functioning. Although multiple broadly distributed brain regions have been implicated in anosognosia, there is a remarkable consistency across diverse conditions suggesting that compromised functioning of the frontal lobe, particularly the right frontal lobe, leads to an increased risk for anosognosia.

Given the extent to which the frontal lobes, and associated high-level cognitive processes, are known to be vulnerable to the ageing process, it seems reasonable to hypothesise that older adults may witness a decline in their ability to appraise their cognitive functioning. In fact, both longitudinal (Nyberg et al., 2010) and cross-sectional (Calin, Diana, Orbelo, & Ross, 2007; Cherry & Hellige, 1999; Clark & Knowles, 1973; Brickman, Zimmerman, Paul et al., 2006; Lu, Rodrigue, Kennedy et al., 2011) studies have documented evidence of greater age-related decline in right over left hemisphere functioning. However, the relationship between metacognitive dimensions and healthy ageing remains poorly understood. Differential age-related effects on processes involved in metacognition have been documented, but these need to be interpreted with caution as few findings have been observed consistently. One finding that seems to be reasonably reliable is that older adults' slower processing speed can account for some age-related differences in metacognitive abilities. This finding accords with the processing-speed theory of cognitive ageing, which was discussed earlier in this chapter (Salthouse 1996; Salthouse & Babock, 1991; Salthouse & Meinz, 1995). There is also some evidence that older adults may be able to use experience to update their self-assessments, but it has been suggested that their revisions may still be less accurate compared to young adults. A limitation that applies to many of the studies that included healthy older adults is that they did not control for the potential influence of primary task performance on measures of metacognition. Measures of metacognitive accuracy such as the gamma correlation are influenced by task performance (Masson & Rotello, 2009), potentially confounding changes in metacognition with age-related changes in other cognitive abilities required for primary task performance. Another potential barrier to drawing more clear conclusions from the work that has been done in this area, is that many of the studies did not screen their samples for cognitive impairment, which is now a convention in studies of ageing (e.g. Deary, Bastin, Pattie et al., 2006). It is therefore possible that pathology-related cognitive impairments in some of the samples may have accounted for metacognitive deficits that were not observed in other studies. Another factor that curtails what can be concluded from the research on healthy ageing, as well as much of the research on clinical populations with anosognosia, concerns the diversity of methods for measuring and operationalising particular metacognitive abilities of interest. Each approach has its limitations, however, and there is still no clear empirically based reason for favouring

one approach over another. Investigations that compare operational definitions within samples in order to assess the convergent validity of the various approaches could be valuable in clarifying some of these issues. In addition, the prevalence of domain-specific deficits in several clinical populations, and possibly also in healthy older adults, speaks to the need for multi-domain assessments that can account for potential heterogeneity in awareness across functional domains to be employed more routinely.

As briefly broached above, assuming that error-related processing contributes to the appraisal of one's performance (Robertson, 2010; Vocat & Vuilleumier, 2010), investigating the integrity of performance monitoring capacities, and particularly conscious error awareness, in healthy older adults may provide important information on the extent to which metacognitive abilities are affected by the natural ageing process. Despite an implicit role for a performance-monitoring system in anosognosia there is surprisingly little documented knowledge of the actual involvement of the neural circuits for performance monitoring in anosognosia. Therefore, the next section proceeds with a separate overview of the cognitive neuroscience literature on performance monitoring.

1.4 Performance Monitoring

A number of indirect findings, dating back to the 1960s, provided some of the first empirical evidence for the existence of a sophisticated system that could monitor, detect, and compensate for behaviour in a manner that would be predicted by Nelson and Narens (1990) model of metacognition. In a series of psychophysics studies, Rabbit (1966a; 1966b; 1969) found that young adults detected and corrected their errors frequently, rapidly and, in some instances, even without conscious awareness, as indexed by discrepancies between error correction rates and retrospective reports of performance. Rabbitt additionally observed that subjects were less prone to an error on a trial following one in which they had previously erred, and that response times were significantly slower for trials subsequent to an error. These observations were assumed to reflect the adoption of a more cautious response mode to facilitate improved stimulus processing and response selection, in the service of reducing the risk of future errors. By extension, these behavioural findings suggested the activity of a specialised neural system, which actively monitors behaviour and signals the need for adjustments to optimise performance.

1.4.1 Neural Basis of Performance Monitoring

Performance monitoring processes, and their implementation in the human brain, have since been investigated extensively, and continue to be the focus of many research projects. Converging evidence from electrophysiological, hemodynamic and brain lesion studies have implicated the posterior mesial frontal cortex (pMFC)- an area that encompasses the anterior cingulate cortex (ACC) and the pre-supplementary motor are (pre-SMA)- as the fulcrum of a neural system involved in performance monitoring (Cohen & van Gaal., 2012; Ridderinkhof, Ullsperger, Crone & Nieuwenhuis, 2004).

Some of the most seminal evidence for a neural instantiation of a performance monitoring system appeared in the 1990s. Two research groups, working independently, discovered that a fronto-centrally distributed negative electrical potential in the human electroencephalogram (EEG) was reliably associated with errors (Falkenstein, Hohnsbein, Hoorman, & Blanke, 1990; Gehring, Goss, Coles, Meyer, & Donchin, 1993). This event-related potential (ERP), hereafter referred to as the error-related negativity (ERN; Gehring et al., 1993), begins at the onset of the electromyographic (EMG) activity preceding the error response and peaks approximately 50-100 ms after response execution (Kopp & Rist, 1999; Gehring et al., 1993). The ERN has been observed following a range of different types of errors, including errors of action (i.e. uninhibited responses to No-go trials; Scheffers, Coles, Bernstein et al., 1996), errors of choice (i.e. erroneous responses in choice reaction time tasks; Holyoyd, Dien & Coles, 1998) and late responses (Luu, Flaisch & Tucker, 2000), and it is independent of stimulus or effector modality (e.g. Holyoyd, Dien & Coles, 1998; Nieuwenhuis, Ridderinkhof, Blom, Band & Kok, 2001). The ERN is not elicited in situations in which subjects have too little information for detecting errors, such as when task stimuli are degraded, but a number of studies have demonstrated that in such undetermined conditions, an ERN-like waveform known as the feedback-ERN, can be evoked through the provision of error feedback (Badgaiyan & Posner, 1998; Holroyd & Coles, 2002; Miltner, Braun & Coles, 1997; Ullsperger & von Cramon, 2003). The fact that error feedback was delivered externally via sensory stimuli in such studies, suggests that these ERPs are independent of the motor system. Indeed, van Schie et al. have shown that in addition to self-generated errors, the ERN is also evoked by observed erroneous behaviour of others (van Schie, Mars, Rogier, Coles, & Bekkering, 2004). In addition to the ERN and feedback-ERN, another similar fronto-central negativity has been reliably linked to novelty, decision uncertainty and high-conflict (the N2 component; for a review see Folstein & Van Petten, 2008). A number of studies using variety of different neuroimaging methods have localised

the generator of all three of these ERPs to the pMFC (Debener, Ullsperger, Siegel et al., 2005; Dehaene, Posner & Tucker, 1994; Gehring & Willoughly, 2002; Luu & Tucker, 2001; O'Connell, Dockree, Bellgrove et al., 2007; Ullsperger & von Cramon, 2001; van Veen & Carter, 2002; Wessel, Danielmeier, Morton & Ullsperger, 2012).

An increasing number of authors advance that the ERN, feedback-ERN and N2 are all at least partially reflective of oscillatory perturbations in the theta band (3-7 Hz) of the EEG (Cavanagh, Frank, Klein & Allen, 2010; Luu, Tucker & Makeig, 2004; Sauseng, Klimesch, Gruber et al., 2007). Consistent with this, medial frontal (MF) theta oscillations have likewise been source-localised to pMFC (Luu & Tucker, 2001), and recent research has shown that MF theta dynamics are not only sensitive to error commission, negative feedback, decision uncertainty and response conflict (Cavanagh et al., 2010; Cavanagh, Cohen & Allen, 2009; Cavanagh, Figueroa, Cohen & Frank, 2011; Cohen, 2014 Cohen & Donner, 2013 Cohen, van Gaal, Ridderinkhof, & Lamme, 2009) they also predict conflict resolution processes, as well as post-error and post-feedback behavioural adjustments (Cavanagh et al., 2009; 2010; Cohen & van Gaal, 2012; Debener et al., 2005; Nigbur, Ivanova & Sturmer, 2011; van de Vijver, Ridderinkhof & Cohen, 2014). A number of comprehensive meta-analyses have additionally confirmed that the pMFC exhibits increased hemodynamic activity in conditions involving error commission, response conflict, decision uncertainty, negative feedback, negative affect, pain, conflict adaptation, post-error accuracy and post-error slowing of response times (e.g. Nee, Wager & Jonides, 2007; Niendam, Laird, Ray et al., 2012; Ridderinkhof et al., 2004; Shackman, Salomans, Slagter et al., 2011). These findings have been further supplemented by evidence of a causal relationship between the pMFC and performance monitoring processes. For instance, lesions to the ACC have been found to attenuate the ERN (Swick & Turken, 2002) and eliminate conflict resolution and post-error slowing effects (di Pellegrino et al., 2007; Maier & di Pellegrino, 2012; Sheth, Mian, Patel et al., 2012; but see Fellows & Farah, 2005).

Based on the above evidence it is clear that pMFC is a critical neural substrate of a system involved in monitoring not only for errors, but also a range of other salient events. However, an ongoing question has concerned the extent to which the role of the pMFC is restricted to monitoring and evaluating, or whether its function generalises to implementing cognitive control? While the evidence cited above would seem to suggest that the pMFC plays a role in the execution of behavioural adaptations, it must be noted that the observed adaptations would only be effectuated to the extent that a monitoring system has already detected conditions that require increased control. Activation of the pMFC invariably co-occurs with activation of several other regions such as the hippocampus (Hester, Barre,

Mattingly et al., 2008; Klein, Neumann, Reuter et al., 2007b), parietal cortex (Hester & Orr, 2012), occipital cortex (Cohen & van Gaal, 2012), anterior insula (Dosenbach, Fair, Cohen, Schlaggar, & Petersen, 2008; Dosenbach, Visscher, Palmer et al., 2006; Seeley, Menon, Schatzberg et al., 2007 Ullsperger et al., 2010), and possibly most consistently the lateral prefrontal cortex (lPFC; Cavanagh et al., 2009; Fassbender, Murphy, Foxe et al., 2004; Hester, Fassbender & Garavan, 2004, Kerns. 2006; Kerns, Cohen, MacDonald et al., 2004). Indeed, according to an influential model, cognitive control is achieved via two interacting systems: one for monitoring and evaluating current demands for control, and another to regulate the requisite levels of control (Botvinick, et al., 2001; Carter & van Veen, 2007; Miller & Cohen, 2001; Norman & Shallice, 1986; Ridderinkhof, et al., 2004). The lateral prefrontal cortex (lPFC) has been widely implicated as a critical neural substrate of the latter of these systems (e.g. Miller & Cohen, 2001; Ridderinkhof, et al., 2004). Studies have shown that pMFC activation on high-conflict and error trials predicts both lPFC activity and adjustments in performance (Kerns, 2006; Kerns et al., 2004), suggesting that behavioural adaptation following pMFC activity is actually the product of co-ordination between the pMFC and the lPFC. Cavanagh et al. (2009) have furthermore shown that error-related theta phase synchronisation between pMFC and lPFC electrode sites predicts post-error slowing on a trial-to-trial basis. Error-related and conflict-related theta synchrony has additionally been observed between pMFC and the occipital cortex (Cohen & van Gaal, 2012) and pMFC and the ventral striatum (Cohen, Axmacher, Lenartz et al., 2009). Such findings have lead to the hypothesis that MF theta oscillations might be the physiological mechanism through which pMFC communicates with lPFC, and other regions involved in implementing top-down control (e.g. Cohen & van Gaal, 2013).

Summary

Substantial evidence has accumulated to implicate pMFC in monitoring performance for negative action outcomes/salient events, and in precipitating a cascade of neural processes that serve to optimise future behavioural outcomes. MF theta oscillations have been identified as a putative mechanism through which the pMFC engages networks for implementing cognitive control. It is readily conceivable how disruption to a system that is involved in monitoring for unfavourable performance outcomes might lead to inappropriate confidence in one's cognitive functioning. Although studies to date have not specifically implicated the pMFC as a neural correlate of anosognosia, a potential role for the medial PFC, which encompasses the pMFC, in mediating awareness of cognitive functioning has been highlighted in several studies (Ries, Jabber, Schmitz et al., 2007; Ries, McLaren,

Bendlin et al., 2011; Rosen, Alcantar, Rothlind et al., 2010; Zamboni et al., 2013). The vast majority of the literature on performance monitoring, however, has not made the distinction between implicit and explicit, alternatively termed, unconscious and conscious, error detection. Considerable evidence suggest that error detection, and even error *correction*, are not necessarily accompanied by conscious awareness of the error (Rabbit, 1966; Rabbit, 2002; Steinhauser & Yeung, 2010). Although the limits of unconscious processing constitutes a contentious topic in cognitive neuroscience research (e.g. Kouider & Dehaene, 2007; van Gaal, de Lange, & Cohen, 2012), it seems likely that the extent to which errors could contribute to knowledge about one's performance would be contingent on them reaching the threshold for conscious access. The following section provides a review of what is currently known about conscious error detection, termed error awareness hereafter.

1.5 Error Awareness

Although a large body of evidence has accumulated on the function and neural substrates of the performance monitoring system, much less is known about the processes that determine error awareness. In this thesis, error awareness is defined as the conscious perception of a failure to achieve a goal. Little is currently known about the extent to which error awareness during moment-to-moment performance might contribute to awareness of cognitive abilities, but it is relevant to note that there is evidence to suggest that the capacity for error awareness is compromised in most clinical populations that are known to present with anosognosia, including TBI (Hart et al., 1998; McAvinue et al., 2005), dementia (Giovannetti, Libon, & Hart, 2002), psychopathy (Brazil et al., 2009), FTD (O'Keeffe et al., 2007), and schizophrenia (Carter, MacDonald, Ross, & Stenger, 2001). Parallel to the potentially important role of error awareness in facilitating accurate appraisal of cognitive abilities, the capacity to recognise errors in the context of everyday activities such as the management of medication and money, the utilisation of electrical appliances, and driving, may have serious implications for older adults' health and safety.

1.5.1 Measuring Error Awareness

Error awareness is typically measured by asking participants to overtly signal their errors with a response that is not required for the primary task. In this way, an error that is signalled is considered to have been consciously perceived ('aware error'), whereas an error that is not signalled is considered to have been missed ('unaware error'). One significant

issue in studying error awareness is that laboratory tasks of error processing are typically characterised by very high levels of error awareness. For instance, it has been found that healthy participants are usually aware of over 90% of their errors on the frequently employed Eriksen Flanker task (e.g. Scheffers and Coles, 2000; Ullsperger & von Cramon, 2006). Accordingly, researchers have been prompted to develop paradigms that are challenging enough to yield a sufficient number of errors that remain unconscious. To date, three types of such paradigms have been employed, each of which of induces unaware errors by interfering with the emergence of awareness in different ways (Ullsperger et al., 2010).

In the first category are oculomotor paradigms, such as the anti-saccade task (Endrass, Franke, & Kathmann, 2005; Nieuwenhuis, Ridderinkhof, Blom, Band, & Kok, 2001), in which participants must shift their gaze in the opposite direction to a peripherally-presented cue. The anti-saccade-task has been found to yield high error rates, and a large proportion of these errors (~50%) remain unconscious. It has been suggested that the reason so many errors remain unconscious on this task could be due to the fact that erroneous saccades are particularly fast, allowing minimal scope for sensory and proprioceptive feedback (Ullsperger et al., 2010).

The second type of paradigm has involved enforcing multiple competing task rules, such that the active maintenance of all rules at all times is quite challenging. Thus, errors relating to the violation of one or more of the task rules may go unperceived. A primary example of this approach is the Error Awareness Task (EAT; Hester, Foxe, Molholm, Shpaner, & Garavan, 2005), whereby participants engage in a variant of a Go/No-go response inhibition task. In this task an error is defined as an instance where a participant fails to withhold from responding to either a stimulus which is the same as the one presented on the previous trial (Repeat No-go), or a stimulus where the word does not match the font colour (Stroop-No-go). Studies have found that approximately 30% of errors are not perceived on the EAT (Hester et al., 2005; O'Connell et al., 2007).

The third type of paradigm requires participants to make judgements about perceptually-degraded stimuli. For example, in studies by Steinhauser and Yeung (2010; 2012) participants were required to identify which of two noisy stimulus-arrays were of higher contrast. In such tasks participants are often uncertain about the accuracy of their responses and miss a number of errors. An advantage of this type of paradigm is that rates of error awareness can be strategically manipulated by adjusting the visibility of the stimuli.

The differences between these error awareness paradigms calls attention to the fact that unaware errors can be caused by a number of different factors. For instance, in tasks

where the visibility of a stimulus is highly degraded (Oliveira, McDonald, & Goodman, 2007; Scheffers & Coles, 2000; Steinhauser & Yeung, 2010, 2012), unaware errors are elicited by introducing high levels of uncertainty about which response is correct. In this case, the participant may be aware of this high uncertainty, but cannot reliably determine the accuracy of their response (Ullsperger et al., 2010). Conversely, for the anti-saccade task, participants would typically have a high degree of certainty about what the correct response should be, but due to the fact that erroneous saccades can be so fast and fleeting, they may be uncertain about whether the correct response was actually executed. Eliciting unaware errors by these means contrasts markedly with how unaware errors arise in paradigms such as the EAT. Here, the stimuli are not difficult to perceive; the perceptual information that is required to make the correct response is always available, but unaware errors arise from a failure to heed the information and implement the appropriate task rules. Correspondingly, Shalgi et al. have hypothesised that aware errors on the EAT are due to failures of response inhibition, whereas unaware errors are due to lapses of sustained attention to the task (Shalgi, O'Connell, Deouell, & Robertson, 2007). As such, it is argued that unaware errors that occur on paradigms such as the EAT are more likely to approximate to the failures of awareness in everyday life.

1.5.2 Neural Basis of Error Awareness

Amidst the profusion of research on error processing, only a small proportion of studies have made the distinction between initial error commission and subsequent error awareness. An influential study by Nieuwenhuis et al. constituted one of the first attempts at examining the neural correlates of error awareness (Nieuwenhuis et al., 2001). As mentioned earlier, errors are reliably associated with a fronto-central negativity (the ERN) that peaks approximately 50-100 ms after the error response (Falkstein et al., 1990; Gehring et al., 1993). The ERN is followed by a later (300-500 ms post-response), more broadly-distributed P300-like component (Ridderinkhof, Ramauter, & Wijnen, 2009), known as the error-positivity (Pe; Falkenstein, Hohnsbein, & Hoormann, 1995; Falkenstein, Hohnsbein, Hoormann, & Blanke, 1991). Nieuwenhuis et al. found that these components were differentially modified by error awareness on an anti-saccade task. Specifically, the ERN was present regardless of whether participants were aware of a given error, whereas the Pe was only present for aware errors (Nieuwenhuis et al., 2001). These findings have subsequently been reproduced in at least eleven other studies using a variety of tasks (Dhar, Wiersema, & Pourtois, 2011; Endrass, Frank, & Kathman, 2005; Endrass, Klawohn, Preuss, & Kathmann, 2012; Endrass, Reuter, & Kathmann, 2007; Hughes & Yeung, 2011;

O'Connell et al., 2007; O'Connell et al., 2009; Pavone, Marzi, & Girelli, 2009; Shalgi, Barkan, & Deouell, 2009; Shalgi & Deouell, 2010).

This robust pattern of results suggests that the ERN and Pe components may reflect dissociable aspects of error processing. Specifically, it has been proposed that the ERN reflects an early rapid, and possibly preconscious detection mechanism that does not discriminate aware from unaware errors, but is sensitive to response conflict (Botvinick, Braver, Barch, Carter, & Cohen, 2001; van Veen & Carter, 2002) or changes in reward probability (Holroyd & Coles, 2002). The Pe, on the other hand, is assumed to be selectively associated with the conscious recognition of an error (Nieuwenhuis et al., 2001; Overbeek, Niewenhuis, & Ridderinkhof, 2005). While there is a large degree of consensus that the ERN is generated in the pMFC (e.g. Luu & Tucker, 2001), the substrate(s) involved in generating the Pe remain less clear. Electrical source localisation studies have highlighted diverse potential generators, including parietal cortex (van Veen & Carter, 2002), posterior cingulate cortex (O'Connell et al., 2007), as well as rostral (van Boxtel et al., 2005; van Veen & Carter, 2002) and caudal anterior cingulate cortex (Herrmann, Rommler, Ehlis, Heidrich, & Fallgatter, 2004; O'Connell, et al., 2007). Given the inconsistency of the results to date, and the limited spatial specificity of source localisation methods, particularly when applied to broadly-distributed ERPs like the Pe, conclusions regarding the contributions of these regions to error awareness must be considered tentative.

At least six ERP studies have now challenged the assertion that the ERN is not modulated by awareness, by showing that the ERN amplitude was significantly more negative for aware errors compared to unaware errors (Hewig, Coles, Trippe, Hecht, & Miltner, 2011; Maier, Steinhauser, & Hubner, 2008; Scheffers & Coles, 2000; Steinhauser & Yeung, 2010; Wessel, Danielmeier, & Ullsperger, 2011; Woodman, 2010). On a similar note, Hughes and Yeung (2011) have shown that error-trials with larger ERN amplitudes also tended to have larger Pe amplitudes. The authors did however point out that the correlation coefficient was relatively modest (*pearson's* r = .228), suggesting that while there may be common information in the ERN and Pe, there is also substantial independent variance in the two components.

A number of hypotheses, relating to study design, stimulus representation, and the operationalisation of error awareness, have been advanced to explain the discrepant findings regarding the extent to which the ERN is sensitive to error awareness (Wessel, 2012; Steinhauser & Yeung, 2010). For instance, Steinhauser and Yeung (2010) have argued that the relationship between the ERN and error awareness that has been found in some studies could be correlational as opposed to causal in nature. They suggest that the greater

magnitude of the ERN for aware errors might be a by-product of higher levels of conflict for aware relative to unaware errors, as opposed to a reflection of its direct role in error processing. This may be particularly applicable in tasks where there is uncertainty regarding the identification of either the target stimulus, or the response that was made. If an individual did not perceive the target stimulus or an incorrect response on a given trial, that trial would be associated with low conflict (low ERN) and unawareness.

On a related note, it has been hypothesised that the ERN component reflects the partial phase-locking of oscillatory activity in the theta frequency band (Luu & Tucker, 2001; Luu, et al., 2003; Luu, et al., 2004; Trujillo & Allen, 2007). As already mentioned above, the ERN and medial frontal (MF) theta have many common features. Both phase-locked MF theta and the ERN have been source-localised to pMFC (Luu & Tucker, 2001; Luu et al., 2004). MF theta power is sensitive to negative feedback, response conflict and error commission (Cavanagh et al., 2009; 2010; 2011; Cohen, 2014; Cohen et al., 2009; Cohen & Cavanagh, 2011; Cohen & van Gaal, 2012; Luu & Tucker, 2001; Luu et al., 2003; 2004; Trujillo & Allen, 2007) and again, like the ERN (e.g. Debener et al., 2005), the magnitude of the error-evoked MF theta response has been linked to post-error behavioural adaptation (Cavanagh et al., 2009; 2010). The most plausible model for ERN generation through ongoing MF theta oscillations suggests that the ERN results from partial phase-locking in the context of an overall increase in MF theta power around the time of the erroneous response (Luu et al., 2004; Trujillo & Allen, 2007). The phase and power of oscillatory signals are orthogonal (Siegel, et al., 2012; Varela, Lachaux, Rodriguez, & Martinerie, 2001), however, and if a proportion of the increase in theta power is not reliably time-locked to the latency of response execution, it will not be captured in the trial-averaged ERP (Luu, et al., 2004). Consequently, it is conceivable that by focussing exclusively on the ERN, information in the MF theta signal relevant to processes such as error awareness may not be accounted for.

The extent to which MF theta is sensitive to error awareness has rarely been investigated to date. Cohen et al. (2009) reported that MF theta power around the time of conscious error commission was significantly greater than theta power during 'unconscious' errors, on a Go/No-go task. However, in this study, unconscious errors were elicited exogenously via backward masking of a No-go cue, therefore, error awareness was likely precluded due to participants not having enough perceptual information to perceive such errors from the outset. In a very recent study, Murphy et al. (Murphy, Robertson, Harty, & O'Connell, under review) have provided the first demonstration of a robust association between MF theta power and the emergence of awareness. They have shown that MF theta

power, elicited during the aforementioned EAT task, not only predicts the emergence of error awareness up to 120 ms before the error is even committed, but also the timing of the error awareness responses. These results indicate that MF theta power, and by extension pMFC activity, may be an important early determinant of error awareness.

Similar to early electrophysiological investigations, initial fMRI studies of error awareness also suggested that the pMFC was not sensitive to error awareness. In two separate studies it was found that the BOLD response in pMFC, the putative generator of the ERN and MF theta, was equivalent for both aware and unaware errors (Hester et al., 2005; Klein, Endrass, Neumann et al., 2007a). Two more recent fMRI studies with significantly larger sample sizes have, however, found that pMFC activation was greater during errors that were followed by awareness compared to errors that were not (Hester, Nandam, O'Connell et al., 2012; Orr & Hester, 2012), suggesting that the previous null findings may have been attributable to insufficient statistical power. It has, nonetheless, been suggested that pMFC alone is unlikely to be sufficient in generating awareness, and that its role in error awareness is probably best understood in relation to activity in other regions (e.g. Orr & Hester, 2012). Several other brain regions, including bilateral PFC, parietal somatosensory areas, and anterior insula have been found to exhibit increased BOLD activity for aware relative to unaware errors (Hester et al., 2005; 2009; 2012; Klein et al., 2007a, Orr & Hester, 2012).

Aside from fMRI studies demonstrating increased BOLD responses in the pMFC and anterior insula for aware relative to unaware errors (Klein et al., 2007a; Hester et al., 2005; Hester et al., 2009), triangulating evidence for a link between these structures and error awareness has come from a number of other sources. For instance, it has been found that changes in heart rate (Wessel, Danielmeier, & Ullsperger, 2011), skin conductance response (SCR; O'Connell et al., 2007) and pupil dilation (Wessel et al., 2011) are all significantly more pronounced for aware compared to unaware errors. The anterior insula has been consistently implicated in the generation and processing of autonomic nervous system responses, such as heart rate (Critchley, Mathias, Josephs et al., 2003; Hajcak, McDonald, & Simmons, 2003; Mutschler, Wieckhorst, Kowalevski et al., 2009), skin conductance response (SCR; Hajcak et al., 2003; Mutschler et al., 2009; Nagai, Critchley, Featherstone, Trimble, & Dolan, 2004) and pupil dilation (Critchley, Tang, Glaser, Butterworth, & Dolan, 2005). The pMFC is consistently co-activated with the anterior insula (Dosenbach et al., 2008; Dosenbach et al., 2006; Ullsperger, 2010; Seeley et al., 2007), and it has been found that pMFC activity correlates with SCRs (Critchley, Elliot, Mathias, & Dolan, 2000; Nagai et al., 2004), heart rate (King, Menon, Hachinski, & Cechetto, 1999; Wager, Waugh, Lindquist et al., 2009), and pupil diameter (Critchley et al., 2005; Murphy,

O'Connell, O'Sullivan, Robertson, & Balsters, 2014). Taken together, these findings suggest a strong link between error awareness, pMFC, and autonomic responses regulated by the anterior insula. However, it is still unclear whether the autonomic responses are a cause, consequence, or correlate of error awareness (Klein, Ullsperger, & Danielmeier, 2013).

1.5.3 Error Awareness as a Decision Process

Hypotheses regarding the function of the ERN and Pe components have typically conceptualised the former as a preconscious error detection mechanism (e.g. Falkenstein et al., 2001; Yeung, Botvinick, & Cohen, 2004) and the latter as reflecting the conscious recognition of an error (e.g. Nieuwenhuis et al., 2001; Overbeek et al., 2005). These hypotheses are more descriptive than explanatory, however, failing to specify how, if at all, earlier processes indexed by the ERN might influence the Pe and the emergence of awareness. Further, they do not clarify whether the Pe is the expression of error awareness, or a reflection of the processes that lead to error awareness (Ridderinkhof et al., 2009). In contrast, the recent conceptualisation of the emergence of error awareness as a decision process (Steinhauser & Yeung, 2010; 2012; Yeung & Summerfield, 2012), offers a mechanistic and potentially integrative account of various factors affecting conscious error recognition.

This framework proposes that the emergence of error awareness involves the continuous accumulation of evidence that an error has been made until enough evidence has accumulated to pass an internal response threshold, or 'decision criterion,' at which point error awareness is achieved. The accumulation of evidence is a noisy process, however, and is highly sensitive to the quality and reliability of the decision evidence. If the evidence regarding a given error is weak or noisy, the amount of accumulated evidence is likely not to reach the decision criterion, and the error will not be consciously recognised (**Figure 1.3**). An important strength of this framework is that it applies long established principles from sequential sampling models derived from mathematical psychology that have demonstrated substantial explanatory power in accounting for behaviour in a wide range of perceptual and cognitive tasks (e.g. Ratcliff, 1978; Ratcliff & Rouder, 1998; Ratcliff & Smith, 2004), and permit particular predictions to be made regarding the underlying neural signal dynamics, as well as how specific manipulations should influence the timing and accuracy of performance. The import of this general approach is particularly supported by the demonstration that the accumulation of perceptual evidence is directly encoded in the firing

rates of specific neuronal populations in association cortices (Gold and Shadlen, 2002; 2007). The innovative aspect of the recent work by Steinhauser and Yeung (2010; 2012) is the application of these principles to a second-order *metacognitive* decision process, i.e. to making a decision about the accuracy of a previous decision or action (Yeung & Summerfield, 2012).

Research grounded in this model has recently suggested that the Pe component directly reflects the accumulation of evidence that an error has been committed. In one study, Steinhauser and Yeung (2010) employed a perceptual discrimination paradigm wherein incentives were varied to encourage participants to adopt a low or high decision criterion for signalling their errors. Based on specific predictions derived from an accumulation-to-bound model, this manipulation enabled the authors to distinguish between neural signals relating to the evidence accumulation process and the production of decision output. They found that while the ERN was not affected by the manipulation, the Pe varied consistently with the decision criterion in a manner that suggested that this component reflects the accumulation of evidence for a previously-committed error. In a second study, the same authors manipulated the speed-accuracy trade-off of the same primary perceptual discrimination task, to test the prediction that the amplitude of the Pe would vary as a function of the strength and latency of the accumulated evidence for an error. Based on prior computational modelling results (Steinhauser, Maier, & Hubner, 2008), they predicted that low speed pressure should be associated with weaker evidence for an error. In accord with this, average Pe amplitude was attenuated, and error signalling was impaired in a low speed pressure condition compared to a high speed pressure condition (Steinhauser & Yeung, 2012). The results of this study were thus also consistent with the hypothesis that the Pe reflects accumulation of evidence that an error has been committed.

The above studies by Steinhauser and Yeung (2010; 2012) provided some of the first evidence that the Pe reflects an accumulation process that *leads to* rather than follows from error awareness, and as such resolved an important question in error awareness research (Ridderinkhof et al., 2009). However, the decision process account of error awareness also entails several specific predictions regarding underlying neural dynamics that were not tested in these studies. If the Pe reflects a decision mechanism, its rate of rise and peak latency should predict the timing and accuracy of decision reports, and it should reach a fixed amplitude immediately prior to the error awareness response, consistent with a boundary-crossing effect or, in other terms, an action-triggering decision threshold (Ratcliff & Smith, 2004). To explore the relationship between peak latency and the timing and accuracy of decision reports, Murphy et al. (2012) have since capitalised on a novel variant of the EAT

that involved speeded awareness signalling. In accordance with the evidence accumulation hypothesis, it was found that the peak latency of the Pe was tightly correlated with the timing of error awareness ($r = .53$, $p < .01$). In fact, the study revealed that the Pe was more tightly time-locked to the awareness response than to the error itself (**Figure 1.5**). Considering the majority of ERP studies on error awareness have measured the Pe component as the amplitude of the average waveform locked to the initial erroneous response, this observation may indeed speak to the need for many previous findings regarding the Pe to be re-evaluated. For instance, the differences in Pe amplitude that have been reported for a range of clinical groups (e.g. Larson & Perlstein, 2009; O'Connell et al., 2009; Perez, Ford, Roach et al., 2011; Olvet, Klein, & Hajcak, 2010) may have been at least partially attributable to delayed or more variable emergence of error awareness (Murphy et al., 2012).

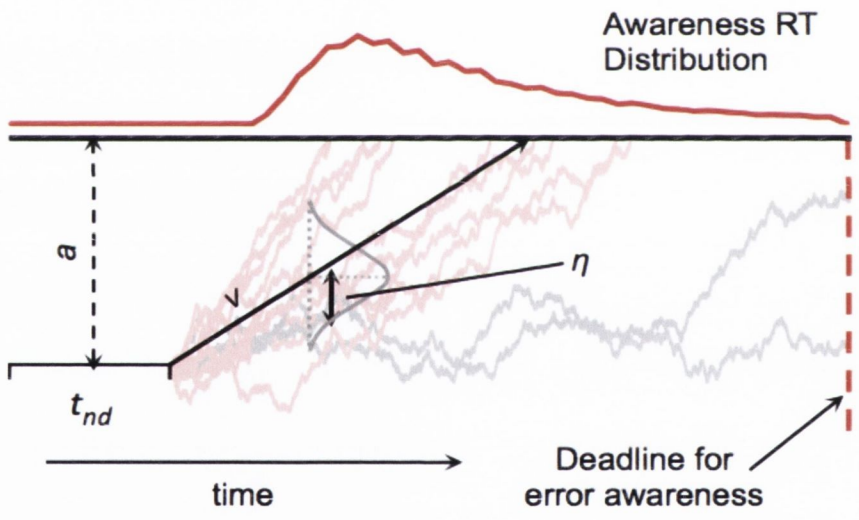

Figure 1.3 Diffusion modelling of the second-order decision process. (**a**) Schematic representation of the one-choice drift diffusion model. Noisy error evidence is accumulated over time at mean drift rate v until a response threshold a is reached (light red traces) or a deadline on detection expires (grey traces). Drift rate is normally distributed across trials with standard deviation η, and non-decision-related processing time is captured by t_{nd}. Upper panel shows simulated awareness response time (RT) distribution (Murphy et al., under review)

The predictions regarding Pe build-up rate as a reflection of evidence accumulation and amplitude corresponding to a decision threshold have also been verified in another

recent study (Murphy et al., under review). Specifically, it was found that the build-up rate of the Pe was significantly steeper for error trials on which awareness was achieved quickly, whereas the *amplitude* of the Pe reached a fixed level irrespective of the speed of the awareness response. Thus, combined with the peak latency finding in the earlier study, these observations indicate that the Pe exhibits the three cardinal defining properties of 'decision variable' signals predicted by decision-making models, and observed in primate (Gold & Shadlen, 2007) and human electrophysiology (O'Connell, Dockree, & Kelly, 2012; Kelly & O'Connell, 2013) for first-order perceptual decisions.

Murphy et al. (under review) have also provided some novel insight into the *nature* of the evidence that forms the input to the error awareness decision process. Existing evidence accumulation accounts specify sensory information as the source of evidence, but the extent to which sensory information in isolation would constitute the evidence for a second-order metacognitive decision process is questionable. Several candidate substrates for second-order decision evidence are suggested from other sources (Ullsperger et al., 2010). Murphy et al. (under review) have demonstrated that an early source of evidence may arise from information encoded in MF theta oscillations, which distinguish between aware and unaware errors from a very early latency relative to error commission, and is also highly sensitive to the timing of the awareness response (**Figure 1.4**). Both of these effects are characteristic of a decision evidence signal (Kelly & O'Connell, 2014; Smith & Ratcliff, 2004). In addition, they also demonstrated that the build-up rate of the Pe mediates the relationship between theta amplitude and the timing of awareness, thus suggesting a strong interaction between MF theta and Pe signals in driving the error awareness process (Murphy et al., under review).

On a related note, numerous neuroimaging studies have shown that the pMFC is engaged in instances involving response conflict (Botvinick, Nystrom, Fissell, Carter, & Cohen, 1999; Carter, Braver, Barch et al., 1998; Ullsperger & von Cramon, 2001), and response conflict is hypothesised to be a critical determinant of MF theta (Cohen, 2014; Cohen & Cavanagh, 2009) and ERN (Danielmeier, Wessel, Steinhauser, & Ullsperger, 2009; van Veen & Carter, 2002; Yeung, Botvinick, & Cohen, 2004) amplitude, and also of the subsequent emergence of error awareness (Yeung et al., 2004). Indeed, in a recent review, Cohen's (2014) description of MF theta as a signature of response conflict is highly compatible with sequential sampling models of decision making. Specifically, he defines response conflict as the competition between two or more conflicting actions when an error could arise. This idea that two different responses may be activated simultaneously is reminiscent of the way sequential sampling models of decision making propose that

evidence is accumulated separately for two alternative choices (correct versus incorrect; e.g. Ratcliff & Smith, 2004). Trials in which both accumulators get close to their threshold, but one wins by a narrow margin, would supposedly evoke levels of post-response conflict/MF theta commensurate with the probability that a mistake was made. Such an interpretation would imply that MF theta is an indirect index of the amount of sensory evidence that has been accumulated for the two alternative choices, and accordingly provides important information for the second-order metacognitive decision process.

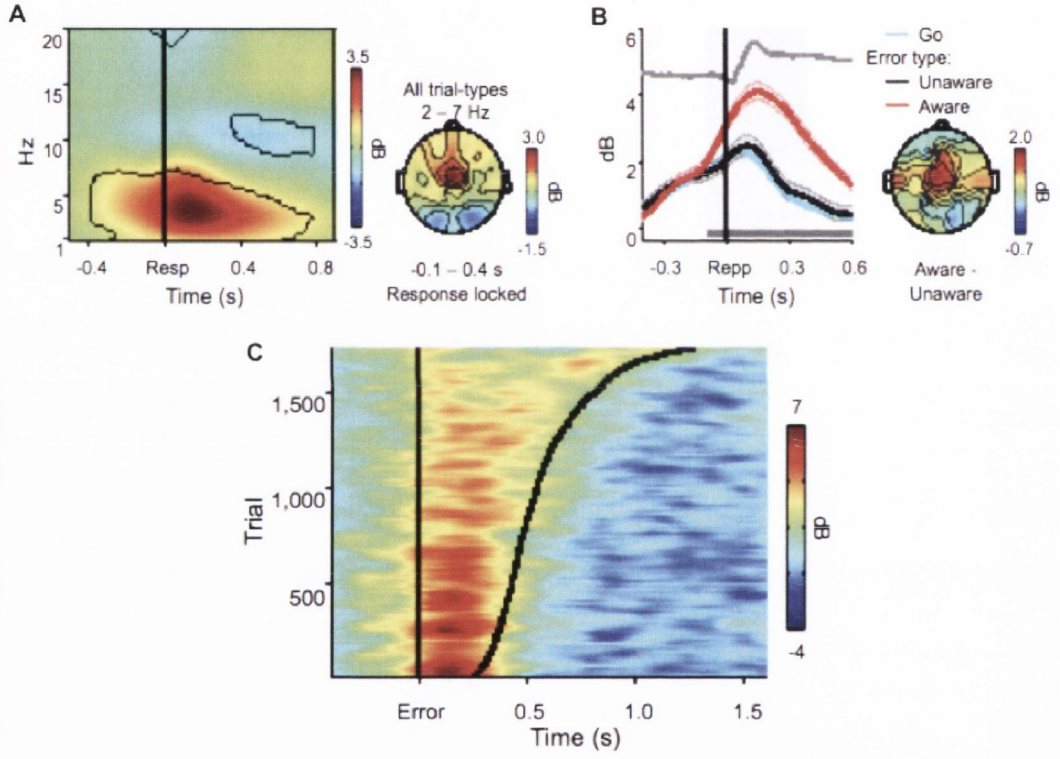

Figure 1.4 Medial-frontal theta-band oscillatory power predicts the accuracy and timing of second-order decisions. (**A**) Time-frequency plot of medial-frontal (MF) power, aligned to the primary task response and averaged across aware error, unaware error and RT-matched go trials; black lines enclose regions of significant power change relative to a pre-stimulus baseline ($p < 0.01$, paired *t*-test). Scalp topography shows theta-band (2-7 Hz) power averaged over all trial types. (**B**) Response-aligned MF theta waveforms separately for each trial type; grey trace is the condition-averaged ERP (arbitrarily scaled). Shaded gray area shows latencies of associated scalp topography. Shaded error bars represent standard error of the mean. Topography illustrates scalp distribution of error awareness effect. (**C**) Single-trial surface plot showing the temporal relationship between the MF theta power and awarenesss RT (curved black line; Murphy et al., under review)

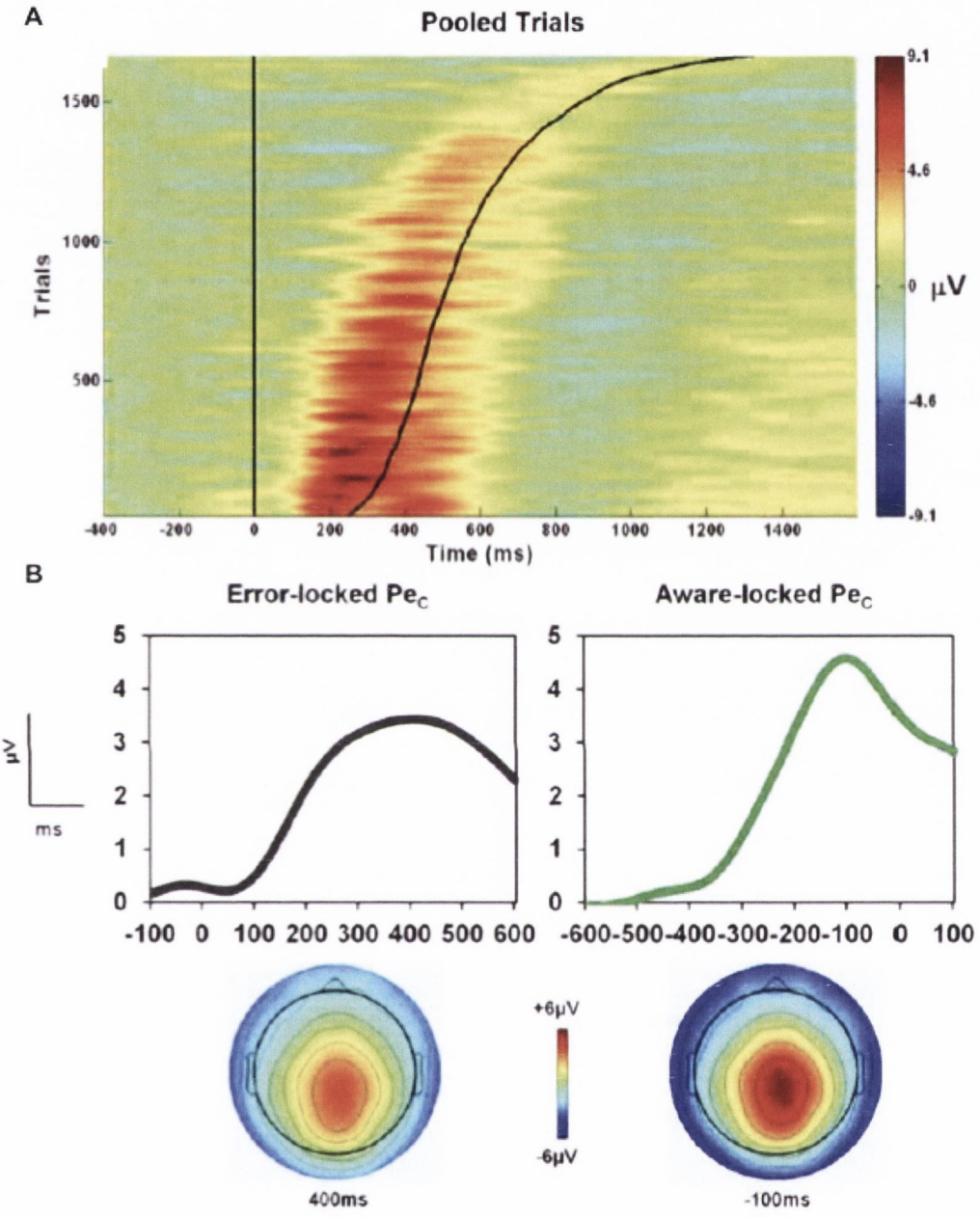

Figure 1.5 Relationship between the error positivity (Pe) and the timing of awareness. (A) Single-trial aware error Pe waveforms locked to the erroneous response, pooled across participants and sorted by awareness response time (RT; black line). Note how Pe peak latency closely tracks awareness RT. **(B)** Group average time-course and topography of the Pe when locked to both the error press and subsequent awareness press on aware error trials. Note the identical topographies but greater component amplitude when locked to the timing of the awareness response. Figure adapted from Murphy et al. (2012).

There is thus considerable support for the idea that the pMFC may provide a modality independent evidence signal that an error has occurred, which is encoded by MF theta, and subsequently accumulated in the Pe component. In contrast to the robust association between MF theta power and the emergence of awareness, Murphy et al. observed no such relationship for the ERN. This observation is consistent with the previously discussed hypothesis that the ERN component reflects the partial phase-locking of MF theta coincident with the erroneous response, and accordingly, due to a significant proportion of the error-related MF theta not being phase-locked to the error, much information originating from the pMFC that may determine error awareness is not captured by the ERN.

It is intuitively plausible that the Pe may also accumulate evidence from other sources aside from pMFC, such as proprioceptive feedback from the erroneous action and interoception of autonomic responses accompanying the error (Ullsperger et al., 2010; Wessel et al., 2011). To reiterate a point made by Ullsperger et al. (2010), the Pe may accordingly constitute a *compound* error signal based on multiple sources of information, that must become sufficiently strong before awareness of the error is achieved.

In sum, compelling evidence now suggests that the Pe reflects the accumulation of evidence that an error has occurred, and MF theta oscillations may provide one source of this evidence. This evidence accumulation framework is particularly appealing because it specifies the precise mechanisms by which error awareness emerges, and places the process within a well-established, well-defined and testable model of the decision process. Of particular relevance to the present thesis, this new level of understanding about the mechanistic nature of MF theta and the Pe means that they have untapped potential to provide novel insights regarding the neural origins of performance monitoring deficits, and perhaps even self-awareness in a broader sense.

1.5.4 Neurocognitive Precursors to Performance Errors

It is important to draw attention to the fact that the vast majority of neuroimaging studies of error-processing have focussed on error-evoked activations, and the neural and behavioural sequelae of errors. However, it is conceivable that performance errors are preceded by maladaptive neural dynamics which predispose toward error commission, and which may dictate whether or not an individual will become aware of an error. Indeed, a

variety of distinct behavioural and neural markers that are predictive of upcoming performance trends have recently been documented. At multiple time-scales, trials preceding errors have been characterised by a speeding of response times (Gehring & Fencsik, 2001; Smith & Brewer, 1995), attenuation of ERPs related to stimulus processing (O'Connell, Dockree, Robertson, et al., 2009; Padilla, Wood, Hale, & Knight, 2006) and performance monitoring (Allain, Carbonnell, Falkenstein, Burle, & Vidal, 2004; Eichele, Juvodden, Ullsperger, & Eichele, 2010; Hajcak, Nieuwenhuis, Ridderinkhof, & Simons, 2005; Ridderinkhof, Nieuwenhuis, & Bashore, 2003), perturbations of oscillatory activity signals in theta and alpha bands related to performance monitoring and attention, respectively (Cavanagh, et al., 2009; Macdonald, Mathan, & Yeung, 2011; Mazaheri, Nieuwenhuis, van Dijk, & Jensen, 2009; O'Connell, Dockree, Robertson, et al., 2009), increased activity in the brain's default mode network (Eichele, Debener, Calhoun et al., 2008; Li, Yan, Bergquist, & Sinha, 2007), and decreased activity in frontal regions associated with the regulation of attention (Eichele, et al., 2008; Weissman, Roberts, Visscher & Woldorff, 2006).

Although this research is beginning to characterise the neural states that predispose toward error commission, markedly little is known about how such factors affect subsequent error processing and conscious error awareness. Thus, while errors of commission may result from either failures of response inhibition or sustained attention, those that arise from the former are likely to be consciously perceived if the sustained attention networks are sufficiently engaged, whereas those that arise from the latter are likely to go unnoticed (Shalgi et al., 2007). A number of studies have indeed previously found that the capacities for sustained attention and error awareness are correlated across individuals (Hoerold et al., 2008; McAvinue et al., 2005; O'Keeffe et al., 2007) and Hester et al. have reported that individuals who are prone to inattentiveness, indexed using a personality scale, have an attenuated pMFC response to errors (Hester, Fassbender, & Garavan, 2004). It is difficult to disentangle sustained attention processes from other processes within error awareness paradigms, but given that sustained attention is known to rely on a relatively well-defined predominantly right lateralised fronto-parietal network (Coull, Frackowiak, & Frith, 1998; Coull, Frith, Frackowiak, & Grasby, 1996; Manly, Owen, Avinue et al., 2003; Singh-Curry & Husain, 2009; Sturm & Willmes, 2001; Sturm, de Simone, Krause et al., 1999), an interesting idea for future research would be to examine the extent to which the activity of this network relates to error awareness, and the morphology of the Pe.

1.5.5 Error awareness in healthy older adults

To date, levels of error awareness in healthy older adults have only been explicitly investigated in two studies (Rabbitt, 1990; 2000; briefly mentioned previously under *Metacognitive abilities in healthy older adults*, this chapter). In the earlier of these studies, 80 participants representing four different age cohorts were administered 600 successive trials on a simple choice response task. Participants were assigned to one of three groups, which were distinguishable based on how they were instructed to handle errors on the task. The "ignore errors" group was instructed to continue with the task as if they had not made an error, the "error correction" group was instructed to promptly correct all errors they committed, and the "error signalling" group was instructed to press a "panic" button when they committed an error. Rates of error commission did not differ among the age cohorts or task conditions, indicating that older adults could perform the primary tasks as proficiently as their younger counterparts. There was also no difference in error correction rates between the age groups. Older adults did, however, demonstrate significantly diminished error signalling relative to young adults. Specifically, participants over the age of 50 signalled significantly less of their errors than young adults, and participants over the age of 70 signalled the smallest proportion of errors of all age groups. Participants were additionally asked to retrospectively estimate how many errors they committed over the course of the experiment. Irrespective of task condition, it was found that all participants underestimated their errors. However, the oldest cohort (aged 70-79) self-reported significantly less errors than the youngest cohort (aged 18-29). Compromised error signalling amidst intact error correction may not seem too unfavourable considering individuals are rarely required to provide commentaries on errors without subsequently correcting them. However, it is unclear whether all error correction responses reflect true error detection or merely a delayed activation of the correct response, without explicit detection of the initial error. Both behavioural and ERP data support a dissociation between explicit error detection and automatic error correction (e.g. Ullsperger & von Cramon, 2006). Moreover, the decreased error signalling in conjunction with the inaccurate retrospective recall of errors, strongly suggested that the ageing process affects the capacity for conscious error awareness.

In a subsequent study employing a similar choice response task, Rabbitt (2002) varied the interval between making a response and having to indicate whether or not it was accurate, which he termed the response-signal interval (RSI). He found that error signalling improved for both young and older adults as RSI durations increased, and error-signalling rates became commensurate at 800 ms for young adults and 1000 ms for older adults. This observation prompted Rabbitt (2002) to re-evaluate his previous findings and conclude that

older adults are as capable of evaluating their errors as young adults when provided with sufficient time. While these studies have offered important insights into ageing and error monitoring they involved a relatively simple experimental task; it is difficult to ascertain from these studies whether older adults would exhibit proportionate error awareness in real life, or when tasks are more cognitively taxing.

A number of electrophysiology studies that did not distinguish between aware and unaware errors have also provided insight on the integrity of error monitoring abilities in healthy older adults. For instance, Band and Kok (2000) suggested that older adults' ability to efficiently monitor their performance was affected by task complexity, as opposed to time constraints. In this study, young and older adults performed a mental rotation task (Cooper & Shepard, 1973) in which they had to report whether characters, rotated clockwise or counterclockwise over 45° or 135° angles, were in a mirrored or normal position. In contrast to results documented for choice response tasks (Rabbitt, 1990, 2002), older adults had a significantly higher error rate relative to young participants, and their accuracy failed to improve over the duration of the experiment. An interesting pattern of results was observed for error correction behaviour within and between the two age groups. Older adults made a significantly larger proportion of immediate corrections of their errors relative to young adults on the 45° condition; however, older adults' error correction rates plummeted for the more cognitively taxing 135° condition, such that they corrected proportionately fewer of their errors relative to young adults. These data imply that task complexity disproportionately impacts on the extent to which error detection and error correction can be achieved in older adults, relative to young adults, and that older adults may display maximal error handling in situations which facilitate automaticity.

It is important to consider what the source of difficulty was for the older adults on the more complex condition. It is possible that older adults could not determine the identity of the target stimuli, and accordingly could not generate an internal representation of the correct response. If so, it is likely that an error on the more complex condition would fail to trigger response conflict or any other hypothetical source of evidence that may contribute to the emergence of error awareness. Therefore, one potential explanation for the observed pattern of results is that there was a shift in the nature of the errors from primarily action slips in the easier condition to proportionately more mistakes, due to insufficient knowledge, in the more complex condition. ERP results in this studies echoed the behavioural data: while older adults' averaged ERN and Pe components were not distinguishable from young adults on the 45° condition, they were significantly reduced on the 135° condition. However, given that the authors did not distinguish between aware and unaware errors, it cannot be

determined to what extent age-related attenuation of the trial-averaged ERN and Pe is truly due to reduced error awareness, or merely to delayed and/or more variable timing in the emergence of awareness. The fact that absolute error rates in this study were not equal across young and older adults also constrains the interpretation of the presence and absence of age-differences in the averaged ERPs. For instance, pMFC activity and ERN amplitude are known to be sensitive to error likelihood and error significance, such that individuals who make less errors (i.e. young adults in the this study) typically exhibit larger ERN on the infrequent occasions when they do make an error (Gehring et al., 1993; Holroyd et al., 2005). Future investigations of performance monitoring and error awareness should accordingly endeavour to control for any potential age-related differences in accuracy on the primary task.

In another study, Falkenstein et al. reported an age-related reduction in ERN amplitude on both a four choice reaction time task and a flanker task. Although they found a reduction in error correction rates for the most complex conditions of the task, there were no significant differences between young and older adults (Falkenstein, Hoormann, & Hohnsbein, 2001). To account for these findings the authors proposed the possibility of a threshold effect with the ERN, such that even though the older adults' ERN were attenuated relative to young adults, they were still sufficient to trigger error detection and subsequent error correction. As noted previously, however, error corrections are not necessarily precipitated by error detection (Rabbitt, 2002; Ullsperger & von Cramon, 2006). Therefore, it is unclear whether the threshold effect hypothesis would have been supported if the authors and had made an explicit distinction between aware and unaware errors.

A number of other studies have found that the amplitudes of both the ERN (Beste, Willemssen, Saft, & Falkenstein, 2009; Endrass, Schreiber, & Kathmann, 2012; Mathalon, Bennet, Askari et al., 2003; Mathewson, Dywan, & Segalowitz, 2005; Nieuwenhuis, Ridderinkhof, Talsma et al., 2002; Schreiber, Pietschmann, Kathmann, & Endrass, 2011) and the Pe (Tays, Dywan, Capuana, & Segalowitz, 2011; Mathewson et al., 2005) are reduced in older adults relative to young adults. But again, for the same reasons outlined above, the lack of an overt indication of awareness prohibits the drawing of any firm conclusions about the integrity of older adults' error awareness capacities. Age-related reductions in post-error MF theta oscillations have also been documented in four studies (Anguera, Boccanfuso, Rintoul et al., 2013; Kolev, Beste, Falkenstein, & Yordanova, 2009; Kolev, Falkenstein, & Yordanova, 2005; van de Vijver, Cohen, & Ridderinkhof, 2014). In light of the recent findings by Murphy et al. (under review), one would predict that reduced MF theta oscillations would be associated with reduced error awareness, but again, since these studies

did not involve overt error signalling it is not yet known whether this is the case. It is also possible that older adults are capable of compensating for this decline in oscillatory activity by recruiting alternative neural networks (cf. Stern, 2000). Another more general limitation that is pertinent to a number of the above mentioned studies is the relative lack of consensus surrounding the definition of "older adult" populations. While 65 is broadly regarded as the lower-bound age benchmark in gerontology literature, the older adults in some of these studies were relatively young. For instance, the age of the sample that Falkenstein et al. (2000) refer to as "older adults" ranged from only 54 to 65. Accordingly, Falkenstein et al.' results, among others (e.g. Band & Kok, 2000) may actually *overestimate* older adults' performance monitoring abilities.

1.5.6 Neuroimaging Methods

As evident from the reviewed literature, research in the field of performance monitoring and error awareness has used two principle techniques: fMRI and EEG. Both techniques have different advantages and disadvantages. EEG can measure the low-voltage changes caused by the electrochemical activity of neurons. EEG is therefore capable of capturing the direct electrical activity in the brain, making the mapping of discrete cognitive processes on their millisecond timescale possible. However, scalp EEG recordings are influenced by complex interactions with the electrical field of the skull and scalp. Thus, the spatial localisation of neuronal activity via EEG is difficult. On the other hand, fMRI provides very high spatial resolution, but limited temporal resolution owing to the fact that the hemodynamic signals lag the corresponding neural activity by several seconds.

In this thesis, EEG was chosen over fMRI as the method for investigating age-related changes in error awareness at the neural level for a number of reasons. First, this thesis aims to capitalise on the recent conceptualisation of error awareness as a decision process to interrogate the neural basis of this capacity in older adults. Although fMRI studies have the potential to provide insight on where evidence signals and decision variables might reside (cf. Heekeren, Marrett, Bandettini, & Ungerleider, 2004), the limited temporal resolution of fMRI is not conducive to testing the critical decision-predictive dynamics that define a decision variable (O'Connell et al., 2012). Similarly, it is apparent that age-related deficits in error awareness may arise from any of many potentially discrete sensory and neurocognitive processes that are closely related in time. The millisecond level timescale of EEG can be particularly useful for disentangling the individual contributions of such processes. Finally, there is evidence to suggest that the cardiovascular response can be

altered in older adults compared to young adults. This can mean that age-related changes in hemodynamic signals may not necessarily reflect a proportional change in the underlying neural activity (e.g. D'Esposito, Zarahn, Aguirre, & Rypma, 1999).

Summary

In comparison to the intensively studied neural substrates of performance monitoring, knowledge of the neural basis of conscious error awareness remains incomplete, and the extent to which the ageing process impacts on the capacity for error awareness is even less well understood again. Much of what is known about error awareness to date has been derived from the study of the two error-evoked ERP components: the ERN and Pe. Establishing what elements of error processing are represented by these ERP components has proven difficult, however (cf. Wessel, 2012). Specifically, questions have endured with regard to how or whether the ERN/pMFC contributes to the error awareness process, and whether the Pe reflects a process that leads to, or follows from, the emergence of error awareness. EEG research grounded in a well-defined mechanistic framework has recently provided convincing evidence to suggest that the Pe reflects the real-time emergence of error awareness and not one of its sequelae (Murphy et al., 2012; Murphy et al., under review; Steinhauser & Yeung, 2010; 2012). As regards the ERN, this work would support the notion that the ERN is driven by the proportion of MF theta oscillatory activity that is phase-locked to error commission, and that while MF theta oscillations themselves appear to be a robust determinant of error awareness, the ERN may not always have the same predictive capacity due to a proportion of MF theta activity not being reliably time-locked to the latency of error commission.

1.6 Overall Summary and Objectives of Thesis

The purpose of this chapter was to provide a review of the relevant literature on cognitive ageing, metacognition, performance monitoring, and error awareness. Coverage of the cognitive ageing literature demonstrated that age-related losses are not necessarily seen across all cognitive functions, but declines in capacities that rely on cognitive control and frontal lobe structures are particularly prevalent. It has been argued that as older adults' cognitive functioning begins to decline, the ability to monitor and evaluate the success of their cognitive processes could have important implications for their ability to calibrate their

daily activities to suit their strengths and weaknesses. Yet, little is known about the impact the natural ageing process has on such metacognitive processes.

The empirical work within this thesis is divided into two parts. The first part (Chapter 2 and Chapter 3) is comprised of behavioural and electrophysiological investigations of the effect of natural ageing on self-awareness and performance monitoring. The second part (Chapter 5 and 6) constitutes investigations of the potential for transcranial direct current stimulation to enhance these capacities in older adults.

More specifically, the main objective of Chapter 2 will be to determine whether older adults demonstrate compromised awareness of their cognitive functioning through a multi-domain assessment of self-awareness. A secondary aim of this chapter will be to explore the relationship between error awareness as measured by the EAT and awareness of daily functioning as measured by the collateral rating method. Primarily, knowledge of this relationship, or lack thereof, may have important implications for understanding the mechanisms of self-awareness (Robertson, 2010; Vocat & Vuilleumier, 2010), but it will also shed light on the ecological validity of the EAT paradigm. Verification of the latter is particularly germane in the context of this thesis as the EAT will be employed extensively throughout the subsequent chapters.

Chapter 3 will constitute the first electrophysiological investigation of error awareness in older adults. Although studies have provided evidence to suggest that the EEG correlates of error awareness are attenuated, none of these included an explicit measure of error awareness. Moreover, in these studies the Pe components were always measured as the amplitude of the average waveform locked to the initial erroneous response. Recent findings by Murphy et al. (2012) have highlighted important limitations of characterising the Pe in this way (see *Error Awareness as a decision process,* this chapter). Heeding this, the variant of the EAT which involves speeded error signalling will be employed, and a number of analyses will be conducted to rule out the possibility that any potential age-related differences in Pe morphology are merely attributable to delayed or more variable timing in the emergence of awareness. Given that MF theta oscillations seem to play an important role in the emergence of error awareness (Murphy et al., under review), age-related differences of this spectral component of the EEG will also be investigated.

Chapter 4 will provide an evaluation of the research on the plastic potential of the ageing brain and the use of transcranial direct current stimulation (tDCS) to enhance cognitive capacities in older adults. Chapter 5 will then present four separate experiments tailored to assess the potential of tDCS to modulate older adults' capacity for error

awareness. Chapter 6 will extend on chapter 5 by acquiring EEG data concurrent to tDCS to characterise the electrophysiological correlates of tDCS induced behavioural changes.

Finally, Chapter 7 will provide a general discussion of the findings in this thesis, their respective implications, and suggestions for future research.

Chapter 2: Multi-domain Assessment of Self-Awareness in Healthy Older adults

2.1 Introduction

All humans are prone to occasional lapses or errors as they engage in their daily activities. Although the errors themselves typically have unfavourable consequences, they can also play a critical adaptive role by signaling to us that current performance levels are not sufficient to attain our goals, and by allowing us to establish accurate impressions of our own abilities. The capacity to monitor performance is particularly important from a clinical perspective, as compromised awareness (SA) of a deficit will necessarily impede the patient in making efforts to recover from it, or implement compensatory strategies. Indeed, numerous studies have documented associations between poor SA of deficits and a range of negative outcomes, including poor motivation for treatment (Fleming, Strong & Ashton, 1996; Malec & Moessner, 2001), increased care-giver burden (Seltzer, Vasterling, Yoder, & Thompson, 1997) and poor general prognosis (David, 1992; McEvoy, Apperson, Appelbaum, & Ortlip, 1989). The natural ageing process is known to have a deleterious effect on a wide range of cognitive functions (Grady, 2012; Heddin & Gabrieli, 2004; McAvinue, Habekost, Johnson, et al., 2012; Salthouse, 1996), rendering older adults more prone to erroneous behaviour (e.g. Burke & Shafto, 2004; Gold, Powell, Xuan, Jicha & Smith, 2010; Young & Bunce, 2011), yet very little research has examined SA of deficits in healthy older adults.

Functional imaging work has suggested that the neural substrates of SA reside across a distributed network of brain regions (Pia, Neppi-Modona, Ricci, et al. 2004; Prigatano & Schacter, 1991; Rosen, Alcantar, Rothlind et al., 2010), but the robust association between compromised prefrontal cortex (PFC) function and SA deficits across several different clinical populations, including traumatic brain injury (O'Keeffe, Dockree, Moloney, Carton, & Robertson, 2007), schizophrenia (David, Bedford, Wiffen & Gilleen, 2012), substance abuse (Hester, Nestor, & Garavan, 2009), Alzheimer's Disease (Starkstein, Vázquez, Migliorelli, et al., 1995), attention-deficit/hyperactivity disorder (O'Connell, Bellgrove,

Dockree, et al., 2009) and focal frontal lesions (Hoerold, Pender & Robertson, 2013), indicates that the PFC is a particularly important component of the SA network. Although the neuropsychological underpinnings of SA have yet to be fully established (Prigatano, 2005) reduced SA has frequently been linked to memory impairment (e.g. Agnew & Morris, 1998; Starkstein et al., 1995; Noe et al., 2005), and several studies have demonstrated a close relationship between SA and sustained attention (for an overview, see Robertson (2010)). Given that the PFC is particularly vulnerable to the effects of ageing (e.g. Heddin & Gabrieli, 2004), and that memory and attentional capacities are known to decline with increasing age (see Balota, Dolan, & Duchek, 2000 for a review), there is basis for hypothesising that the capacity for SA may be reduced in older adults.

A small number of studies have suggested that older adults demonstrate a diminished ability to monitor and appraise performance (Bruce, Coyne, & Botwinick, 1982; Graham, Kunik, Doody, & Snow, 2005; Rabbitt, 1990; Suchy, Kraybill, Frnachow, et al., 2011), but others have provided some evidence to the contrary (Clare, Whitaker, & Nelis, 2010; Lovelace & Marsh, 1985; Rabbitt, 2002). Overall, the research on SA in healthy ageing is not conclusive, and of particular import, these studies have not measured SA across a range of cognitive and behavioral domains, which is important given the potential domain specificity of SA deficits (e.g. Hart et al., 2005; Hart, Sherer, Whyte et al., 2004; Prigatano & Altman, 1990). The present study aims to address this gap in the literature by employing the first multi-domain assessment of SA in healthy older adults.

The most common method for measuring SA in patient populations is to examine the discrepancy between self-reports and informant-reports on questionnaire measures of daily functioning, with the premise that a discrepancy in the direction of the informant reporting more difficulties indicates impaired SA (Fleming, Strong & Ashton, 1996; Hart et al., 2004). SA was examined in terms of attentional control, memory functioning and socio-emotional functioning, respectively, using this questionnaire discrepancy score method. A computerized measure of SA that required participants to overtly signal their errors (i.e. demonstrate online error awareness) during a neuropsychological task was also administered. A number of authors have argued that online error awareness enables recognition of difficulties as they occur, and may therefore contribute to broader aspects of SA in daily life (Jenkinson, Edelstyn, Drakeford, & Ellis, 2009; Larson & Perlstein, 2009; Ownsworth & Fleming, 2005; Robertson, 2010). However, such a relationship has yet to be established empirically, and was accordingly identified as an important question for the current study. A battery of neuropsychological tests were also administered to obtain cognitive profiles of the participants and to examine the relationship between SA and other cognitive domains.

Given that SA is linked to PFC function, as well as cognitive capacities such as attentional control and memory, all of which are known to deteriorate with increasing age, it was hypothesised that older adults would have diminished SA relative to young adults. We also predicted that online error awareness would be associated with questionnaire measures of SA, and that SA would correlate positively with sustained attention and memory capacities.

2.2 Methods

Participants

Fifty-one older adults and 47 young adults took part in the study. Four older adults were excluded because their Mini-Mental State Examination (MMSE, (Folstein, Folstein & Hugh, 1975) score indicated possible cognitive impairment (<24). Two older and two younger adults were also excluded due to poor accuracy on the Error Awareness Task (<30% correctly withheld no-go trials). As a result, the final sample consisted of 45 younger adults (31 female) with a mean age of 22.7 years (SD 4.9, range 18-34) and 45 older adults (29 female) with a mean age of 76.2 years (SD 7.1, range 66-90). Exclusion criteria were visual impairment, history of psychiatric illness, neurological insult, drug or alcohol abuse, and/or reporting current use of antipsychotic or antidepressant medications. The most common illnesses for which older adults were taking medication for were hypertension (n=10), osteoporosis (n= 5), arthritis (n= 5), and hypothyroidism (n= 4). All participants were asked to refrain from consuming caffeine on the day of testing. Procedures were approved by the ethical review board of the School of Psychology, Trinity College Dublin in accordance with the Declaration of Helsinki, and all participants provided informed consent.

Background Measures

A number of background neuropsychological tests and measures were administered to all participants. These included: The Mini-Mental State Examination (MMSE), the National Adult Reading Test (NART; Nelson, 1982; Nelson and Willison, 1991), Logical Memory 1 (immediate recall) subtest of the Wechsler Memory Scale (WMS-III; Wechsler, 1997), a test of verbal fluency (animal naming), the Sustained Attention to Response Task (SART; Robertson et al., 1997), and a two-choice reaction time task (CRT). Participants also completed the Hospital Anxiety and Depression Scale (HADS; Zigmond and Snaith, 1983) to assess symptoms of anxiety and depression.

For both the SART and the CRT, stimuli were presented on a Dell Latitude Laptop using E-prime 2.0 software (Psychology Software Tools, Inc, PA, USA). For the SART, the numbers 1 to 9 appeared in a fixed sequence and participants were required to make a left button click for every number except for the number three. Participants completed two blocks of the task, each of which included 25 No-go targets (the number 3) and 200 Go trials (all other numbers). The CRT was included as a measure of speed of processing. Each trial of the CRT started with the participant holding down a white central button on a RB-530 response box (Cedrus, San Pedro, CA, USA) to trigger target onset. Participants were then required to make a speeded press of a 'green' button if the target 'YES' appeared on screen or a 'red' button if the target 'NO' appeared. They were instructed to return to the white button after target offset to trigger the next target. To guard against pre-emptive responding target offset could not be achieved if the white button was released before the target appeared. The task comprised 50 'NO' trials and 50 'YES' trials presented in random order. The interval between depression of the white trigger button and the target onset varied between 800ms and 1100 ms. The task was self-paced, but participants were instructed to respond quickly and accurately. Speed of processing was measured in milliseconds and was split into a 'cognitive response' measured as time from target onset to trigger offset (release of white key) and 'motor response' measured as time from trigger offset to response selection (depression of green key or red key).

Measures of Self-Awareness

The Error Awareness Task (EAT; Hester, Foxe, Molholm, Shpaner, & Garavan, 2005) was used as a measure of online error awareness, and questionnaire measures of daily functioning included the Cognitive Failures Questionnaire (CFQ; Broadbent, Cooper, Fitzgerald, & Parkes, 1982), the Socio-Emotional Questionnaire (SEQ; Bramham, Morris, Hornak, Bullock, & Polkey, 2009) and the Memory Awareness Rating Scale, Memory Functioning Scale (MFS; Clare *et al., 2002*).

The Error Awareness Task

The EAT is a Go/No-go response inhibition task in which participants are presented with a serial stream of single color words, with congruency between the semantic meaning of the word and its font color manipulated across trials (**Figure 2.1**). Participants were trained to respond with a single speeded left mouse button press (A) in situations where the meaning of the word and the font color in which it was presented were congruent (Go-trial) and to withhold this response when either of two different scenarios arose: (1) when the word presented on the current trial was the same as that presented on the preceding trial (Repeat

No-go trial), and (2) when the meaning of the word and its font color did not match (Incongruent No-go trial). In the event of a commission error (failure to withhold to either of these No-go trials) participants were trained to signal their "awareness" by making a right mouse button press (B) *on the subsequent trial.* In these instances they were not required to make their standard Go-trial response. The next standard Go-trial after an error was thus rendered irrelevant which guarded against the possibility that some errors may fail to reach awareness because ongoing processing has been interrupted by the onset of another stimulus (Rabbitt, 2002).

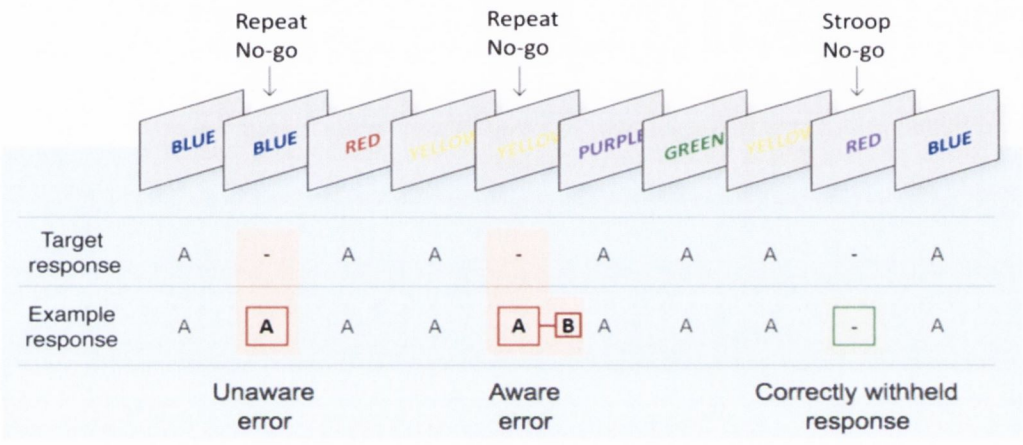

Figure 2.1 The Error Awareness Task Participants were required to make a speeded button press ("A") to all congruent stimuli and to withhold from responding to incongruent stimuli (Stroop No-go) or when a word was repeated on consecutive trials (Repeat No-go). In instances where participants failed to correctly witthold a response, they were required to press a separate button ("B") on the subsequent trial to signal error awareness.

In addition, due to concerns that group differences in online error awareness on this task might arise purely from group differences in the number of errors made, a feature that adaptively modified levels of difficulty was integrated into the task. This entailed checking the participants' accuracy over consecutive periods of 40 trials and adapting the stimulus duration accordingly. The first 40 stimuli of the task were always presented for 750 ms and were succeeded by an inter-stimulus interval (ISI) of 750 ms. The stimulus duration subsequently remained at 750 ms as long as accuracy on the previous 40 trials was between 50% and 60%. However, if accuracy exceeded 60% the stimulus duration and ISI were set to 500ms and 1000ms respectively for the subsequent 40 trials. If accuracy fell below 50%, the stimulus duration and ISI were set to 1000ms and 500 ms respectively. This evaluation and task adjustment occurred every 40 trials thereafter. All participants performed four blocks of

the task, consisting of 225 word presentations, 200 of which were Go trials and 25 of which were No-go trials (12 Repeat No-gos and 13 Incongruent No-gos, or vice versa). The duration of each block was approximately 5.6 min. It was ensured that all participants were well-practiced and fully understood the requirements of the task before they began their first block.

CFQ. The CFQ is a 25–item scale that includes statements relating to levels of attentional control in daily life. It has been employed in a broad range of clinical and non-clinical populations and has high construct validity (e.g. Larson et al., 1997; Wallace, Kass, & Stanny, 2002; Wallace & Vodanovich, 2003). The specificity of the CFQ as a measure of attentional control, rather than global cognitive function, is borne out by research indicating that the scale is not correlated with general intelligence but is robustly correlated with objective indices of attention (Manly, Robertson, Galloway & Hawkins, 1999; Robertson et al., 1997; Tipper & Baylis, 1987). Higher CFQ scores indicate poorer perceived attentional control.

MFS. The MFS is comprised of 13-items that ask about individuals ability to perform memory tasks in a range of everyday situations. The scale has been validated in healthy ageing and early stage Alzheimer's Disease (Clare, Whitaker & Nelis., 2010). Higher MFS scores indicates better perceived memory functioning.

SEQ. The SEQ is a 30-item scale that includes statements relating to the recognition of basic emotions, empathy with the expression of these emotions, relationship skills and public behavior. The SEQ has demonstrated reliability and validity in brain injury patients (Bramham et al, 2009) and healthy adolescents (Wall, Williams, Morris & Bramham, 2011). Higher scores indicate poorer perceived socio-emotional functioning.

Each of the questionnaire measures of awareness was rated for identical items by participants and an informant. All informants were aged between 20 and 64 years (Mean 48.16, SD 10.59), had known the participant for 2 years or more, and had spent 6 hours or more with the participant in the 2 months preceding completion of the questionnaires. Discrepancy scores were calculated correcting for differences in direction of scoring. The difference between self-ratings and informant ratings were divided by the mean of the two sets of ratings to prevent scaling effects from distorting the measurement (Clare, Whitaker, & Nelis, 2010; Clare, Whitaker, Nelis, et al., 2011). Corrected discrepancy scores close to zero indicate good agreement between the participant and the informant. For all three

measures, positive scores indicated that the informant reported more difficulties than the participant, and vice versa.

Statistical Analysis

All of the neuropsychological tests, as well as performance indices on the EAT were analyzed using one-way ANOVAs. Normality was assessed using the Shapiro-Wilk test, and where necessary the appropriate transformation was applied to the data. Due to the fact that response times (RT) to Go-trials following a No-go trial were likely to be disrupted by error-signalling responses, trials up to n+1 relative to the error-signalling response were excluded from the Go-trial RT analysis. For the questionnaire measures of SA, univariate ANCOVAs were performed on each of the corrected discrepancy scores with Age Group (two-level) as the between subjects factor. Significant group differences were found for speed of cognitive response, speed of motor response, anxiety and depression, therefore all of these variables were entered as covariates. Significant main effects ($p<.05$) were followed up with Bonferroni adjusted paired and independent samples t-tests to determine the origin of the effect of Age Group. All reported effects were significant regardless of whether the covariates were included or not.

To examine, the interrelationships between the different domains of SA, and the extent to which the domains of SA related to the cognitive capacities for sustained attention, memory and verbal fluency, one-tailed Bonferroni adjusted partial correlations were conducted, controlling for speed of cognitive response, speed of motor response, anxiety and depression. Again, all reported effects were significant regardless of whether the covariates were included or not.

2.3 Results

The demographic and neuropsychological data for both groups are summarized in **Table 2.1**. The groups were successfully matched for sex ($\chi^2(1) = .20, p = .655$) and years of education ($F(1,88) = .076, p = .783$), but there was a trend towards an age-related difference in estimated IQ ($F(1,88) = 3.63$, p = .060). Young adults reported higher levels of anxiety ($F(1,88) = 20.19, p < .001$) and depression ($F(1,88) = 11.40, p < .01$) than older adults. Significant effects of Age Group were observed for all of the background neuropsychological tests. Older adults had significantly lower MMSE ($F(1,88) = 23.36, p < .001$), memory ($F(1,88) = 25.69, p < .001$), sustained attention ($F(1,88) = 10.60, p < .01$) and verbal fluency ($F(1,88) = 38.43, p < .001$) scores than young adults. Older adults also had a

slower cognitive response ($F(1,88) = 46.75$, $p < .001$) and slower motor response ($F(1,88) = 75.80$, $p < .001$), compared to young adults. Thus, although all participants were within the normal range for healthy older adults, older adults showed the expected age-related decline in cognitive function.

Table 2.1 Demographic and neuropsychological data for both age groups: mean (SD)

	Young Adults (n=45)	Older Adults (n=45)
Age	22.70 (4.87)	76.16 (7.06)
Age Range	18-34	66-90
Sex	14 Male, 31 Female	16 Male, 29 Female
Years of Education	14.93 (1.16)	15.10 (3.61)
HADS: Anxiety*	6.34 (3.14)	3.61 (2.60)
Depression*	3.61 (1.92)	2.07 (2.37)
NART estimated IQ	112.42 (5.82)	115.04 (7.17)
MMSE*	29.36 (1.00)	28.24 (1.17)
Logical Memory (Delayed recall)***	46.10 (8.13)	37.49 (7.99)
SART: % No-go trial accuracy**	88.73 (8.90)	82.09 (10.26)
Go-trial response time (ms)***	257.27 (31.03)	352.22 (67.49)
Verbal Fluency (Animal Naming)***	30.67 (6.95)	22.91 (4.72)
CRT: Cognitive Response (ms)***	358.74 (51.83)	456.96 (81.23)
Motor Response (ms) ***	549.74 (67.36)	729.94 (121.40)

***$p<.001$; ** $p<.01$; * $p<.05$.

Do older adults show a deficit in self-awareness?

To test the hypothesis that older adults would show a deficit in SA, group differences in the Error Awareness Task, and discrepancy scores on the CFQ, MFS and SEQ were examined.

Error Awareness Task

Performance indices for the EAT are summarized in **Table 2.2.** In order to maximize the number of trials in our analyses, and because there was no Age Group × Target Type interaction for error awareness ($p = .818$), Repeat No-go's and Incongruent No-go's were not dissociated for any analyses. There were no significant group differences in accuracy ($p = .659$), as would have been expected given that task difficulty varied as a function of accuracy, but older adults required significantly longer stimulus durations than young adults ($F(1,88) = 6.14$, $p < .05$) to attain such levels of accuracy (**Figure 2.2**). Older adults also had significantly slower reaction times for go trials ($F(1,88) = 109.03$, $p < .001$) .

Despite comparable accuracy levels, older adults were aware of a substantially smaller percentage of their errors (57.17%) compared to younger adults (81.83%), even when error signalling responses were accepted up to three trials following an error, and when stimulus duration, estimated IQ, speed of cognitive response, speed of motor response, anxiety and depression were controlled for ($F(1,80) = 14.06$, $p < .001$).

Table 2.2 Performance indices on the EAT for both age groups: mean (SD)

	Young Adults (n=45)	Older Adults (n=45)
Mean Stimulus Duration (ms)*	696.05 (157.47)	775.58 (138.16)
Accuracy (%)	60.27 (12.47)	59.29 (10.29)
Repeat Accuracy (%)	72.11 (13.99)	66.75 (11.68)
Colour accuracy (%)	48.42 (14.86)	51.80 (13.88)
Error awareness (%) * **	81.83 (15.35)	57.17 (21.01)
Repeat Awareness (%)**	79.74 (16.79)	53.69 (20.22)
Colour Awareness (%)**	86.70 (14.55)	61.43 (24.46)
Mean Go-Trial RT (ms)***	423.54 (62.11)	563.58 (60.80)

***$p<.001$; ** $p<.01$; * $p<.05$

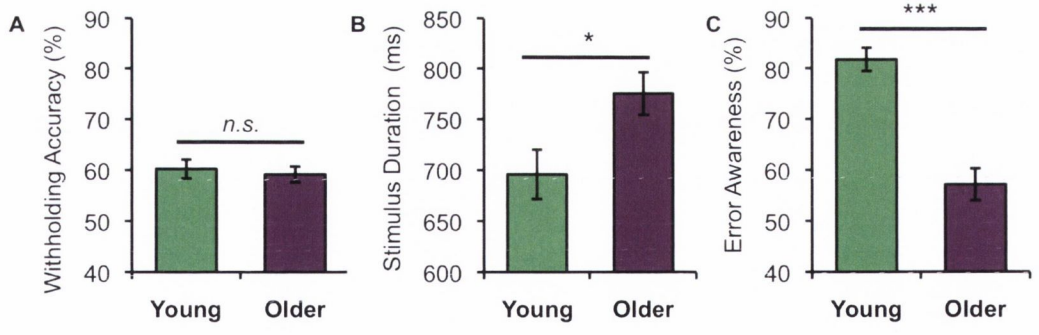

Figure 2.2 Performance indices on the EAT for both age groups. There were no group differences in withholding accuracy (A), but older adults required longer stimulus durations than young participants to attain such levels of accuracy (B). Despite comparable accuracy levels, older adults were aware of a substantially smaller percentage of their errors relative to young adults (C).

Questionnaire Measures of Awareness

The mean ratings for all participants and informants, as well as the associated discrepancy scores on the CFQ, MFS and SEQ are presented in **Table 2.3**.

Table 2.3 Questionnaire measures of awareness. Mean (SD) self-ratings, informant-ratings, corrected discrepancy scores, and estimated marginal means of corrected discrepancy scores for the CFQ, the MFS and the SEQ.

		Younger Adults (n=45)		**Older Adults** (n=45)	
	Min-Max	Mean (SD)	Range	Mean (SD)	Range
CFQ self	0-100	40.84 (12.53)	20-61	41.04 (10.98)	21-58
CFQ informant	0-100	36.56 (16.04)	5-68	47.89 (15.45)	12-78
MFS self	0-52	40.93 (5.74)	26-52	41.77 (6.10)	29-52
MFS informant	0-52	44.57 (6.02)	30-52	34.56 (7.44)	19-51
SEQ self	30-150	66.91 (11.45)	42-84	66.88 (13.42)	39-95
SEQ informant	30-150	68.60 (14.14)	39-94	69.27 (15.59)	39-101
Corrected Discrepancy Scores					
CFQ-D		-.20 (.37)	-1.20 - .56	.13 (.32)	-.67 - .74
MFS-D		-.01 (.20)	-.40 -.44	.17 (.30)	-.29- .77
SEQ-D		.02 (.17)	-.33- .33	.03 (.27)	-.84 - .48
Estimated Marginal Means of Corrected Discrepancy Scores					
CFQ-D		-.14(.36)		.12 (.32)	
MFS-D		-.09 (.20)		.17 (.30)	
SEQ-D		.02 (.17)		.02 (.27)	

CFQ. There was a main effect of Group on CFQ-D ($F(1,80) = 9.63$, $p = .003$), indicating an age-related change in discrepancy scores (see Figure 2). Planned comparisons indicated that older adults reported significantly fewer difficulties with attentional control relative to their informants ($p < .025$), whereas young adults did not differ from their informants ($p > .025$). As seen in Table 3, these group differences were driven by changes in informant reports ($p < .025$) as opposed to self-reports ($p > .025$).

MFS. There was also a main effect of Group on MFS-D ($F(1,80) = 20.49$, $p < .001$). Planned comparisons indicated that that older adults reported significantly fewer difficulties with memory functioning relative to informants ($p < .025$). Young adults, on the other hand, reported significantly more difficulties with memory functioning than informants ($p < .025$). Again, these group differences were driven by changes in informant reports ($p < .025$) as opposed to self-reports ($p > .025$).

SEQ. In contrast to the CFQ and MFS findings, there was no main effect of Age Group on SEQ-D ($p > .05$). As seen in **Table 2.3** there was good agreement between both

younger and older adults self-reports and informant reports, suggesting that age does not have a significant effect on awareness of social functioning.

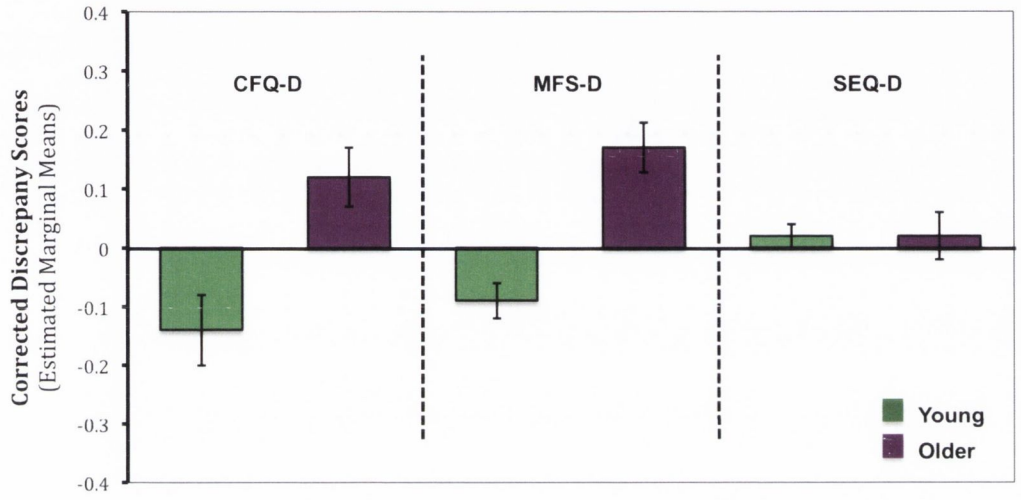

Figure 2.3 Questionnaire discrepancy scores. Corrected discrepancy scores (displaying estimated marginal means that take into account the covariates) for young and older adults on the Cognitive Failures Questionnaire, Memory Functioning Scale and Socio-emotional Questionnaire. Young participants reported more difficulties with attentional control relative to informants, whereas, older adults reported fewer difficulties with attentional control relative to informants (CFQ-D). Young adults also reported more difficulties with memory functioning relative to informants, whereas older adults reported fewer difficulties relative to informants (MFS-D). Both groups of participants showed close agreement with their informants for socio-emotional functioning (SEQ-D).

In order to verify the accuracy of the informants' reports the correspondence between the informant's CFQ and MFS ratings and participants' performance on the SART and Logical Memory 1 were examined. There was a significant negative relationship between participants' performance on the SART and informants' rating on the CFQ ($r = -.49$, $p < .001$), indicating that participants who performed better on the SART were perceived by their informant to have fewer problems with attentional control in daily life. There was a significant positive relationship between participants' performance on Logical Memory 1 and informants' rating on the MFS

(r= .46, p< .001), indicating that participants who performed better on Logical Memory 1 were perceived by their informants to have fewer memory problems in daily life.

Is online error awareness related to awareness of daily functioning?

To test the hypothesis that online error awareness would be related to awareness of daily functioning as measured by the CFQ, MFS and SEQ, partial correlations were conducted controlling for group, estimated IQ, speed of cognitive response, speed of motor response, anxiety and depression (see **Table 2.4**). Online error awareness was correlated with CFQ-D (r = -.43, p < .001) and MFS-D (r = -.29, p = .009). CFQ-D and MFS-D were also correlated with each other (r = .37, p = .001).

Table 2.4 Partial correlations controlling for group. Partial correlations between error awareness and corrected discrepancy scores with group, speed of cognitive response, speed of motor response, anxiety and depression partialled out.

	Measure	1.	2.	3.	4.
1.	**Online Awareness (EAT)** Partial *r*	———			
2.	**CFQ-D** Partial *r*	-.42*	———		
3.	**MFS-D** Partial *r*	-.30*	.34*	———	
4.	**SEQ-D** Partial *r*	-.17	.20	.19	———

• p<.017.

To determine whether the relationships between the different measures of awareness were present within each group independently, partial correlations controlling for speed of cognitive response, speed of motor response, anxiety and depression were conducted for the young and older adults separately for each group (see **Table 2.5**). For the young adults online error awareness was significantly correlated with CFQ-D (r = -.35, p = .016). For older adults online awareness was

significantly related to CFQ-D (r = -.49, p = .001) and MFS-D (r = .37, p = .014). CFQ-D and MFS-D were also correlated with each other (r = .59, p < .001).

Table 2.5. Partial correlations for each group separately. Partial correlations between online awareness and corrected discrepancy scores with speed of cognitive response, speed of motor response, anxiety and depression partialled out for young adults (A) and for older adults (B)

Measure	1.	2.	3.	4.
1. **Online Awareness (EAT)**				
Partial *r*	____	.35*	.11	-.01
2. **CFQ-D**				
Partial *r*	-.49*	____	.10	-.05
3. **MFS-D**				
Partial *r*	-.37*	.59*	____	.14
4. **SEQ-D**				
Partial *r*	-.15	.30	.18	____

Note. Partial correlations for young adults are presented above the diagonal (n=45), and partial correlations for older adults are presented below the diagonal (n=45)
* p<.017

How does self-awareness relate to other neuropsychological measures?

To test the hypothesis that self-awareness would be specifically related to sustained attention and memory capacities, partial correlations were conducted between online awareness, CFQ-D, MFS-D, SEQ-D, sustained attention, memory and verbal fluency, while controlling for the effects of group, estimated IQ, speed of cognitive response, speed of motor response, anxiety and depression. Online awareness was correlated with sustained attention (r = .33, p < .008). No relationship survived Bonferroni correction when the partial correlation analyses were conducted for each group independently.

2.4 Discussion

This is the first multi-domain assessment study of self-awareness (SA) in healthy older adults. As predicted, the results revealed significant impairments in SA in older adults,

as measured by online error awareness and questionnaire discrepancy scores measures. Older, compared to young, adults were aware of 25% less of their errors on the Error Awareness Task even though their performance accuracy was matched to that of young adults, and older adults also under-reported attentional lapses and memory failures in daily life relative to observations by a significant other. These deficits could not be attributed to group differences in speed of cognitive response, speed of motor response, anxiety or depression. We also found that online error awareness was significantly correlated with questionnaire discrepancy scores measures, suggesting that awareness of performance on this laboratory measure is representative of awareness on real world tasks. Finally, consistent with our previous data and predictions (e.g. Hoerold et al., 2008; O'Keefe et al., 2007; McAvinue et al. 2005, Shalgi et al 2007; Robertson, 2010), we found online error awareness to be specifically correlated with sustained attention capacity, but not with other measures of cognitive function such as memory and verbal fluency.

This is not the first study to identify a deficit in online error awareness in healthy older adults. Some earlier work had also indicated that ageing impacts on the ability to signal performance errors (Rabbitt, 1990). However, in a subsequent study, Rabbitt (2002) demonstrated that as the response signal interval (RSI) duration increased beyond 150ms, older adults showed correspondingly greater improvements in error signaling, and actually achieved levels of performance that were on par with young adults when the RSI was increased to 1000ms. It was argued that the previously observed impairments may have been due to the ubiquitous phenomenon of age-related cognitive slowing as opposed to specific deficits in conscious performance monitoring: older adults may not have had enough time to consciously recognize and signal their errors before the onset of the next stimulus (Rabbitt, 2002). However, the task employed in Rabbitt's studies was a self-paced serial choice reaction time task, which may not have been sufficiently complex to simulate the cognitive demands imposed by many daily life situations. Our current findings indicate that older adults do have significant deficits in online error awareness compared to young adults when assessed using a relatively complex task with multiple requirements, even when error-signaling responses were accepted up to three trials following a commission error, and when controlling for general speed of cognitive response, speed of motor response, anxiety and depression. Furthermore, the real-life validity of laboratory measures can only be verified by establishing that they relate to indices of daily functioning, as demonstrated in this study.

It was important to determine that informants provided objective ratings, as is assumed by the discrepancy score method. Significant within-age-group correlations were observed between informant reports of daily life functioning (attention and memory) and

performance on the corresponding neuropsychological tests. These findings indicate that the informant reports were unlikely to have been affected by age-related stereotypes or other biases, and substantiate the validity of the discrepancy scores as indices of SA. Older adults significantly underestimated their difficulties with attentional control and memory functioning relative to informants, whereas young adults overestimated their difficulties relative to informants, albeit only significantly so for memory functioning. This suggests that there are systematic differences between self- and informant-ratings of cognitive functioning in both age groups. In fact, underestimation of abilities amongst high performers is a relatively well-documented finding, which some authors have attributed to a tendency for high performers to compare their proficient performance with an ideal criterion (Hodges, Regehr, & Martin, 2001; Kruger & Dunning, 1999; Kruger & Meuller, 2002). More importantly, underestimation of cognitive abilities is arguably less serious than overestimation, with the latter being more likely to imperil one's safety.

One previous study that used the MFS with healthy older adults found no evidence of reduced awareness of memory functioning (Clare et al., 2010). However, the older adults in the present study were substantially older than those of Clare et al. (average of 7.15 years older and with a lower age bound of 11 years older), and we observed a positive correlation between age and MFS-D indicating that discrepancies increased with age. Further research is required to explore the time-course of age-related SA changes across a wider age range.

In contrast to measures of cognitive functioning, there was close agreement between participants and informants' ratings of socio-emotional functioning for both age groups. The relative accuracy of SA for socio-emotional functioning compared to SA for cognitive functioning suggests that the ageing process is not associated with global SA deficits. This finding is compatible with several other reports of striking dissociations between the accuracy with which various clinical populations appraise some domains of functioning relative to others (e.g. Hart, Sherer, Whyte et al., 2004).

It is worth considering that much variance in socio-emotional functioning is related to non-cognitive personality traits (e.g. Mavroveli, Petrides, Sangareau, & Furnham, 2009), which may remain relatively stable during the ageing process (Starratt & Peterson, 1997). It is accordingly plausible that representations that older adults had of themselves in their younger years with respect to socio-emotional functioning may continue to be accurate into late life, independent of changes in the capacity to self-monitor. In line with this hypothesis, the capacity for online error awareness was not related to SA for socio-emotional functioning, while it was significantly related to SA for both attentional control and memory functioning.

The significant relationships between online error awareness and awareness of cognitive functioning lends credence to the view that online error awareness contributes to general representations of abilities (Jenkinson, Edelstyn, Drakeford, & Ellis, 2009; Larson & Perlstein, 2009; Ownsworth & Fleming, 2005; Robertson, 2010). Accordingly, it may be the case that older adults have failed to notice their lapses and errors as they occurred and as a result are not cognizant of the need to update their self-concept in accordance with the onset of cognitive senescence. This would also explain why older adults' reports of attentional control and memory functioning did not differ from those of young adults.

Consistent with previous findings (e.g. Hoerold et al., 2008; O'Keefe et al., 2007; McAvinue et al. 2005, Shalgi et al 2007), we also found a relationship between sustained attention and online error awareness. These findings corroborate the view that being in an appropriate state of vigilance is an important requisite for recognizing errors as they occur, and in turn for accurate SA (Robertson, 2010). By extension deficits or lapses in sustained attention may be the fundamental phenomenon underlying SA deficits (Robertson, 2010).

It is possible that levels of online error awareness may have been influenced by individual differences in response strategy when performing the EAT. For instance, older adults may have prioritized the primary task of withholding to No-go trials over the secondary task of signaling errors of commission. Based on our current data it is not possible to determine whether and to what extent older adults may have adopted a different response strategy. However, we contend that the observed correlation between performance on the EAT and two measures of awareness of cognitive functioning in daily life suggests that reduced levels of online error awareness reflect a cognitive deficit in older adults and not differences in response strategy. Nevertheless, further electrophysiological investigations of the covert neural correlates of performance on the EAT should be carried out to further our understanding of the deficit and clarify whether young and older adults employ different response strategies.

An additional potential driving factor behind age-related changes in SA is the defense mechanism of denial. However, McGlynn and Kaszniak (1991) have argued that if defensive denial was important, one might expect more mildly demented patients, who are beginning to undergo changes to cognitive abilities, to show the greatest SA deficits, yet there is evidence that inaccuracy increases with the severity of dementia (e.g. Agnew & Morris, 1998). Also, in the present study the discrepancy scores for attentional control and memory functioning were significantly related to online error awareness, which was measured in an objective manner. Collectively, these findings suggest that denial is unlikely to have played a major role in the observed age-related differences in SA.

In conclusion, the data suggest that older adults have significant impairments in SA of cognitive functioning as revealed by converging findings across measures of online error awareness, awareness of attentional control and awareness of memory functioning. This is consistent with age-related structural and functional deterioration of the PFC, and is also consonant with the observations of attenuated electrophysiological correlates of error processing and error awareness (e.g. Mathewson et al., 2005). The observed SA deficits are of considerable significance as self-perceptions of abilities are likely more influential in determining many of the choices of independently living older adults, irrespective of objectively determined levels of performance. Older adults with inaccurate SA may be at risk of choosing activities beyond their abilities, and are also likely to lack the impetus to compensate for declining cognitive function, or actively engage in activities that have been shown to reduce the risk of dementia, such as cognitively demanding activities and physical activity (e.g. Wang, Xu, & Pei, 2012). Investigating the potential to train older adults to become more accurate at appraising their abilities seems like an important pursuit for future research. Indeed there is basis for hypothesizing that addressing self-awareness deficits would confer benefits to other cognitive domains by either eliciting intrinsic motivation for implementing compensatory strategies, or fostering readiness for engaging in, and adhering to, therapeutic interventions. Although the present findings suggest that lapses in attention may be the critical phenomena underlying older adults awareness deficits, further work investigating the specific processing impairments that precipitate unaware errors is recommended. Electrophysiological investigations that incorporate an explicit error signaling response and have the potential to parse out the discrete sensory and cognitive components involved in error processing and error awareness will be an important vehicle for furthering this understanding.

Chapter 3: The Electrophysiological Basis of Deficient Error Awareness in Healthy Older Adults

3.1 Introduction

The findings from Chapter 2 have suggested that in addition to online error awareness being important for remedial actions following errors, as well as safety, in the short-term (Nieuwenhuis, et al., 2001; Klein et al., 2007a, Wessel et al., 2011), the capacity for error awareness may also have implications for the accuracy with which individuals appraise their cognitive abilities. This is particularly significant in light of the associations that have been documented between impaired awareness of deficits and a range of unfavourable outcomes, including engagement in risky behaviour (Cotrell & Wild, 1999; Starkstein et al., 2007), increased care-giver burden (Seltzer et al., 1997), poor motivation for treatment (Fleming et al., 1996; Malec & Moessner, 2001) and poor general prognosis (David, 1992; McEvoy et al., 1989). Consequently, there is a strong imperative for research to elucidate the neural basis of error awareness deficits, and to make use of this knowledge to develop targeted interventions.

As highlighted in chapters 1 and 2, the field of electrophysiology has provided particularly important insight into the neural basis of error awareness. In event-related potential (ERP) studies, error commission on a wide range of neuropsychological tasks reliably evokes two ERP components. The first of these is the error-related negativity (ERN), a fronto-centrally distributed negative waveform seen to peak approximately 50-100 ms after an erroneous response, while the second is the error positivity (Pe), a slower positive waveform which peaks 300-500 ms post-response and is maximal over centro-parietal regions. While there is a large degree of consensus that the ERN is generated in the pMFC, the substrate(s) involved in generating the Pe remain less clear (Ullsperger et al., 2014).

Due to the consistent observation that the Pe is only present on trials where individuals are aware of their errors, is has been assumed that it reflects the conscious

processing of errors. However, the specific neural mechanism underlying the Pe has been a matter of considerable debate (Leuthold & Sommer, 1999; Nieuwenhuis et al., 2001; Overbeek et al., 2005; Ridderinkhof et al., 2009; Shalgi et al., 2009). Recently, a number of studies have provided new evidence to support the hypothesis that the Pe reflects the accumulation of internal evidence that an error has been committed (Murphy et al., 2012; Murphy et al., under review; Steinhauser & Yeung, 2010; 2012). Drawing on long established principles from sequential sampling models developed in mathematical psychology (e.g. Ratcliff, 1978; Ratcliff & Rouder, 1998; Ratcliff & Smith, 2004), this framework proposes that the emergence of error awareness is driven by a decision process, involving the accumulation of evidence for an erroneous response, until enough evidence has accumulated to pass an internal decision criterion.

The question of what constitutes the source, or sources, of evidence that contribute to the emergence of awareness has only begun to be addressed recently. It has been proposed that the Pe likely represents a compound second-order decision signal based on multiple sources of information that must become sufficiently strong before awareness of the error is achieved (Ullsperger et al., 2010). Plausible sources of evidence include continued post-error sensory processing, proprioceptive feedback from the erroneous action, and interoception of various autonomic responses accompanying the error (Ullsperger et al., 2010; Wessel et al., 2011). Authors have also highlighted pMFC generated response conflict as a putative determinant of error awareness and a potential decision evidence signal (Steinhauser et al., 2008; Yeung et al., 2004). Similarly, a number of authors have proposed that MF theta oscillations, which have been source localised to the pMFC (Luu & Tucker, 2001; Luu et al., 2004), encode response conflict emerging from competition between two or more conflicting actions (e.g. Cohen, 2014; Cohen & Cavanagh, 2011). This idea is reconcilable with how sequential sampling models of decision making maintain that for a given decision, evidence is accumulated by two separate accumulators, in favour of opposing choices. Instances where one accumulator wins by a narrow margin would supposedly be accompanied by high levels of response conflict/MF theta corresponding to the likelihood that the wrong choice was made, and accordingly serve as error evidence.

In accord with this, Murphy et al. (under review) have acquired data that suggests that MF theta oscillations may constitute one source of evidence that drives the emergence of error awareness. Specifically, they have demonstrated that the power of the MF theta signal, distinguishes between aware and unaware errors from a very early latency relative to error commission, and is also highly sensitive to the timing of the awareness response, both of which observations are characteristic of a decision evidence signal (Smith & Ratcliff, 2004).

In contrast, Pe amplitude did not predict the timing of awareness, and instead, analogous to the boundary crossing effect that is characteristic of decision signals (Kelly & O'Connell, 2014), it reached a fixed amplitude at the timing of awareness. In addition, they also demonstrated that the build-up rate of the Pe mediates the relationship between theta amplitude and the timing of awareness, thus suggesting a strong interaction between MF theta and Pe signals in driving the emergence of error awareness. These observations are compatible with the idea that the pMFC provides a modality independent evidence signal that an error has occurred, which is encoded by MF theta power, and subsequently accumulated in the Pe component.

In comparison to the Pe, the functional significance of the ERN remains less clear. For many years it was broadly assumed that the ERN reflected an early rapid, and possibly preconsious detection mechanism that did not discirminate aware from unaware errors, but was sensitive to response conflict (Botvinick, Braver, Barch, Carter, & Cohen, 2001; van Veen & Carter, 2002) or changes in reward probability (Holroyd & Coles, 2002). However, a number of studies have now accrued that suggest that the ERN may also be sensitive to error awareness (Hewig et al., 2011; Maier et al., 2008; Scheffers & Coles, 2000; Steinhauser & Yeung, 2010; Wessel et al., 2011; Woodman, 2010). Several issues relating to study design, stimulus representation, and the operationalisation of error awareness may have a role in determining the extent to which the ERN is sensitive to error awareness (cf. Wessel, 2012; Steinhauser & Yeung, 2010). Regardless of whether the ERN discriminates aware from unaware errors, it does not exhibit any clear association with the error awareness decision process (Steinhauser & Yeung, 2010; Steinhauser & Yeung, 2012). It has been hypothesised that the ERN reflects the partial phase-locking of MF theta coincident with the erroneous response (Luu & Tucker, 2001; Luu, et al., 2003; Luu, et al., 2004; Trujillo & Allen, 2007). Due to a significant proportion of the error-related MF theta not being phase-locked to the error, much information originating from the pMFC may not be captured by the ERN. Consequently, it is conceivable that by focusing exclusively on the ERN, information in the MF theta signal relevant to error awareness may not always be accounted for (Navarro-Cebrian, Knight, & Kayser, 2013).

To date, no EEG study has explicitly examined error awareness in healthy older adults. A number of studies have reported that the amplitudes of both the trial-averaged error-aligned ERN (Band & Kok, 2000; Beste et al., 2009; Falkenstein et al., 2001; Endrass et al., 2012; Mathalon et al., 2003; Mathewson et al., 2005; Nieuwenhuis et al., 2002; Schreiber et al., 2011) and Pe (Capuana et al., 2011; Mathewson et al., 2005) of older adults are reduced, relative to young adults. However, given that these studies did not involve an

overt measure of error awareness it cannot be determined to what extent attenuation of these components corresponds to deficits in error awareness. For instance, it is not possible to infer whether the reduced trial-averaged Pe is due to diminished rates of error awareness, or an age-related attenuation of the Pe that that would also be evident when aware error trials are analysed in isolation. Further, given that it has recently been demonstrated that the peak latency and amplitude of the Pe, is more closely locked to the timing of the awareness response than to the timing of error commission (Murphy et al., 2012), attenuation of the error-aligned Pe could also be attributable to greater variability in the timing of the emergence of awareness as opposed to failures of awareness per se. A related limitation that pertains to all of these studies is that they only measured the *averaged* amplitude of the Pe waveform, which fails to capture much of the inherent variability in component amplitude and latency that may be evident at the single-trial level (Bland et al., 2011; Debener et al., 2006; Eichele, et al., 2010).

Age-related declines in grey and white matter density (Burzynska, Preuschhof, Bäckman, et al., 2010; Mann, Hazlett, Byne et al., 2011), and glucose-related metabolic activity (Pardo, Lee, Sheikh et al., 2007) in the pMFC, in addition to reductions in post-error MF theta oscillations (Anguera et al., 2013; Cummins & Finnigan, 2007; Kolev et al., 2009; Kolev et al, 2005; van de Vijver et al., 2014) have previously been documented in a number of studies. In light of the recent findings by Murphy et al. (under review), one would predict that reduced MF theta oscillations would be associated with reduced error awareness, but again, since these studies did not involve overt error signalling it is not yet known whether this is the case.

The accumulation-to-bound framework is particularly appealing because it specifies the precise mechanisms by which error awareness emerges, and places the process within a well-established and testable model of the decision process. In this sense, the accumulation-to-bound framework may provide a particularly fertile ground for examining deficient error awareness in older adults. Specifically, together with EEG and error signalling measures, this framework affords the scope to determine whether older adults' error awareness deficits are attributable to impairments at the sensory, decision, or motor level of processing. Accordingly, in the present study it was of interest to examine the two main ERP components associated with early sensory processing, the P100 and N100, the error-related components, the ERN and Pe, as well as the timing and variability with which the error-signalling response was executed.

Computational modelling studies that have invoked accumulation-to-bound priniciples, have suggested that older adults' slower and less accurate performance of

perceptual tasks results from their tendency to adopt a higher decision criterion, and not from a problem encoding or accumulating the basic sensory evidence (Forstman, Tittgemeyer, Wagenmakers et al., 2011; Ratcliff, Thapar, & McKoon, 2006; 2010; Starns & Ratcliff, 2010; Strayer, Wickens, & Braune, 1987). Although these studies were concerned with perceptual decision making, if their results generalise to second-order metacognitive decisions then older adults would be expected to exhibit higher Pe amplitudes than young adults on error trials that were subsequently signalled.

3.2 Materials and Methods

Participants

Thirty-one healthy older adults and 30 healthy young controls participated in the study. Two older adults were excluded because their Mini-Mental State Examination (MMSE; Folstein, Folstein, & McHugh, 1975) score indicated possible cognitive impairment (<24). Two older and two young adults were excluded due to poor accuracy on the task (<30% correctly withheld No-go trials). A further 4 older adults were excluded because they had insufficient error trials (i.e. less than 12 aware and/or less than 12 unaware errors) following artifact rejection to enable EEG analysis (Larson, Baldwin, Good & Fair, 2010; Olvet & Hajcak, 2009). Accordingly, the sample consisted of 23 older adults (15 female) with a mean age of 71.2 (*SD* 6.38, range 65-88) and 28 younger adults (14 female), with a mean age of 23.37 (*SD* 5.4, range 18-35). Exclusion criteria were left-handedness, visual impairment, history of neurological or psychiatric illness, neurological insult, drug or alcohol abuse, and/or reporting current use of anti-psychotic or anti-depressant medications. All participants were asked to refrain from consuming caffeine on the day of testing. Procedures were approved by the Trinity College Dublin ethical review board in accordance with the Declaration of Helsinki, and all participants provided written informed consent.

The Error Awareness Task

A slightly different version of the EAT was employed in this study to facilitate comparing the data from the older adults with data from a sample of young adults which had previously been collected using this particular version of the EAT. This variant of the EAT differed from that described in Chapter 2 with respect to four features: 1) The Go-trials

constituted "*Incongruent*" as opposed to "Congruent" stimuli, and participants were required to withhold to their responses for "*Congruent* " and "Repeat" trials as opposed to "Incongruent" and "Repeat" trials (*see* Figure 3.1); 2) Participants made their responses using a Microsoft Sidewinder Controller as opposed to a computer mouse and they were instructed to use the thumb of their right hand for both the "A" and "B" button presses; 3) when participants made an error, they were required to signal their awareness of their error by pressing the "B" button *as quickly as possible,* as opposed to waiting until the subsequent trial; 4) Stimuli were consistently presented for 400 ms and followed by an inter-stimulus interval of 1600 ms, irrespective of accuracy on the primary task .

All subjects were administered as least six blocks of the EAT. Where possible (allowing for subjects' willingness and time constraints), more blocks were administered to maximize the number of error trials available for analysis. On average, older adults completed 7.9 (*SD* 0.9) blocks (range 6-10), while young adults completed 9.5 (*SD* 0.7) blocks (range 8-10). Although the data are not reported here, subjects' pupil diameter was recorded throughout task performance (Eyelink 1000, SR Research). Subjects rested their head on a table-mounted head-rest which fixed their distance from the computer monitor at 80cm for the duration of the task in order to minimise head and eye movements.

It was ensured that all subjects were well-practiced and fully understood the requirements of the task before they began their first block.

Data Acquisition and Pre-processing

Continuous EEG data were acquired using an ActiveTwo System (BioSemi) from 64 scalp electrodes in accordance with the standard 10/20 setup, and digitized at 512Hz. Horizontal and vertical eye movements were recorded using two horizontal EOG electrodes placed at the outer canthus of each eye and two vertical electro-occulogram (EOG) electrodes positioned above and below the left eye, respectively. EEG data were processed using custom scripts in MATLAB drawing on EEGLAB formulae for reading data files and spherical spline interpolation of noisy channels (Delorme & Makeig, 2004). The EEG data were re-referenced offline to the average reference. Epochs of 7.7 seconds were extracted around each no-go target trial (-4.2 to 3.5 s) and baseline corrected relative to the .25 second interval preceding the target. The epochs from all blocks for each participant were then concatenated. Extracting such large epochs facilitated the application of the time-frequency analysis to a sufficiently large window (see below). In a preliminary artifact rejection stage, trials were rejected if any scalp channel exceeded an absolute value of 250μV at any time

during the epoch. Independent components analysis (ICA) was subsequently conducted on the remaining epochs to remove blinks and eye movements based on visual scrutiny of component topographies and time courses (Debener et al., 2007, 2008). A high pass filter cut-off of 0.5 Hz was applied to the data to facilitate the implementation of the ICA, but the acquired weights were subsequently back-projected on to the raw data, upon which only a low-pass filter of 40 Hz was applied. A final rejection criterion was applied whereby any trials for which one or more of the channels used to measure the Pe or ERN exceeded an absolute value of 100μV were eliminated. The epochs were then converted to current source density (CSD; Kayser & Tenke, 2006) to increase spatial selectivity and minimize volume conduction.

ERP Analysis

ERP analyses were carried out on four components of interest: the P100, N100, ERN and the Pe. The grand-average peak latency and amplitude of the P100 were defined as the timing and amplitude of the most positive voltage between 50 and 110 ms relative to target stimulus onset. The grand-average peak latency and amplitude of the N100, which directly follows the P100, was defined as the timing and amplitude of the most negative voltage between 130 and 190 ms. Consistent with other studies (e.g. Brodeur, Bacon, Renoult et al., 2008; Murray, Wylie, & Higgins, 2002), these measures were extracted over the occipital electrodes that showed the greatest deflections at these latencies based on inspection of the grand-averages. These electrodes were P7, P8, P9 and P10 for the young adults, and P07, P08, P9, and P10 for the older adults. The grand-average peak latency and amplitude of the ERN were derived from electrode FCz, and were defined as the timing and amplitude, respectively, of the minimum voltage in the 100 ms following the error (Capuana et al., 2011; Falkenstein et al., 2001; O'Connell et al., 2009).

Grand-average measures of build-up rate, peak latency, and amplitude of the Pe were extracted separately for waveforms locked to erroneous responses on No-Go trials (error-aligned) and to the awareness press (awareness-aligned). In the context of the accumulation-to-bound account of error awareness each of these measures corresponds to a specific parameter of the decision process: A) Build-up rate reflects the rate at which evidence is accumulated by the second-order decision process; B) Peak latency reflects the time at which the decision process is concluded and will be determined by the combination of the lag between error commission and the onset of evidence accumulation, the build-up rate and

decision threshold; C) Peak amplitude reflects the decision threshold that is placed on the evidence accumulation process.

Given that the Pe is typically derived from the centroparietal electrodes with the maximal positive deflection (Groom, Cahil, Bates et al., 2010; Mathewson, Dywan, & Segalowitz, 2005), the grand-average spatial topographies were inspected to determine the specific centroparietal electrode sites over which the Pe component was maximal for each group. Electrodes sites P2 and Pz for the young adults reflected the region of maximum amplitude for the young adults, whereas PO3 and POz (see **Figure 3.3**). The average signal across these respective electrode sites was thus used to derive the Pe measures in each group. The peak amplitude, peak latency and build-up rate of the component were otherwise defined in the same way for all subjects. Pe peak amplitude was defined as the mean voltage within 250 ms to 450 ms post-error in the error-aligned average waveforms and within -200 ms to 0 ms relative to the awareness report in the awareness aligned grand-average. Pe peak latency was defined as the time point at which the maximum amplitude was observed within a window spanning from 150 ms to 800 ms post-error in the error-aligned grand-average and within -400 ms to 0 ms relative to the awareness report in the awareness aligned grand-average. The build-up rate of the Pe was measured as the slope of a straight line fitted to the waveform of each subject using a window from 150 ms to 300 ms post-error in the error-aligned grand-average, and a window from -300 to -150 ms relative to the awareness report in the awareness aligned grand-average.

Single-trial measures of Pe peak latency, amplitude, and build-up rate were extracted and averaged for each participant to further characterise the dynamics of the Pe and their relationship with Mean Awareness RT in each age group. A 6 Hz low-pass filter was applied to mitigate the noise inherent in these single-trial measures (Spencer, 2005). Single-trial peak latency and amplitude were defined as the timing and amplitude, respectively, of the maximum voltage from 200 ms post-error press to the slowest awareness press for each participant. Build-up rate was defined as the slope of a straight lined fitted to each single-trial Pe in the 100 ms window preceding the peak latency of each trial.

Time-Frequency Analysis

Single-trial waveforms aligned to correct standard go, unaware error and aware error trials were decomposed into their time-frequency representations through complex Morlet wavelet convolution using the *newtimef* function in EEGLAB (Delorme & Makeig, 2004). This approach computes spectral power at various time points within each epoch using a

sliding window. Time-frequency analysis was applied to the entire epochs (7.7 s) in order to maximize the potential to estimate power at lower frequencies and to circumvent contamination of the time-range of interest by edge artifacts (Cohen & van Gaal, 2013). Signal power and phase were calculated by convolving the wavelets with the single-trial data across 90 linear-spaced frequencies ranging from 1-30 Hz. To account for the trade-off between temporal and frequency resolution, a group of complex Morlet tapered wavelets were computed such that two cycles were used at the lowest frequency increasing linearly up to 12 cycles at the highest frequency. Power was normalized by conversion to decibel (dB) scale (10*log10[power/baseline]), where 'baseline' was defined as the across-trial average power at each frequency increment from -300 to 0 ms prior to stimulus onset, and was derived and applied separately within each trial-type (go, unaware error, aware error). Using a trial-type-specific baseline period ensures that any observed effects of trial-type are not driven by pre-stimulus differences in power. Conversion to a dB scale ensures that data across all frequencies, time points, electrodes, conditions and subjects are on the same scale and are thus visually and statistically comparable (Cohen & van Gaal, 2012; Grandchamp & Delorme, 2011).

This procedure was initially applied to all electrodes across all trial types and revealed a prominent burst in theta (2-7 Hz) power around the time of response (see **Figure 3.4a**), which was maximal over the same electrode used to characterize the ERN (FCz). Accordingly, MF theta power was derived from FCz, and was defined as the mean power of the average waveforms for each trial type from -200 to 500 ms relative to the response. Importantly, selection of channels and time-frequency boundaries by means of the average event-related spectral perturbation across all trial types meant that this process was not biased by any potential trial-type differences (Cohen & van Gaal, 2012). Single-trial MF theta power on aware error trials was defined as the mean power from -100 to 400 ms relative to error commission.

Statistical Analysis

For all behavioural and EEG variables, values which deviated more than 3 standard deviations from the mean were identified and excluded from all subsequent analyses. Performance on the EAT was analysed with respect to accuracy, error awareness, standard go-trial response time (RT), error RT, and Mean Awareness RT. Trials where the awareness press occurred after the onset of the next stimulus were counted as an aware error when

calculating participants' average behavioural measures of error awareness, but were omitted from all ERP analyses. In order to maximize the number of trials for analyses, and because there was no Age Group × Target Type interaction for error awareness (p = .2), no distinction was made between Repeat and Congruent No-go trials. One-way ANOVA with Age as a between-subjects factor were conducted to compare the age groups on performance indices of the EAT, as well as average and single trial measures of the Pe. A two-way repeated–measures ANOVA was used to assess the effect of Alignment (error-aligned versus awareness aligned) on amplitude for each Age Group (young versus older). Two-way repeated measures ANOVA were also used to test for the presence of an awareness effect on the P1, N1, ERN and MF theta. For the P1, N1 and ERN analyses the within-subjects factor was Error-type (aware, unaware) and for the MF theta analyses the within-subjects factor was Trial-type (correct standard go, aware error, unaware error). Significant main effects (p < .05) were followed up with paired and independent samples t-tests. Between subject partial correlations (partial r) were used to examine the relationship between the dynamics of the Pe and MF theta at the per-subject average single-trial level and behavioural measures of error awareness (Mean Awareness RT; Error Awareness), while controlling for the effect of age group. Per-subject average single trial measures were employed for these analyses to provide a finer representation of the Pe and MF theta dynamics. To compare the correlation coefficients obtained for each group separately in a manner that controlled for the different sample sizes, a Fisher's z-transformation (Fisher, 1921) of the Pearson's r values was performed and the level of significance was determined.

3.3 Results

Behavioural data

Performance indices for the EAT are summarised in **Table 3.1**. There was no significant group difference in Accuracy (p = .89). However, replicating the findings of Chapter 2, older adults demonstrated significantly poorer Error Awareness (F(1,49) = 4.5, p = .039), and exhibited both slower (F(1,49) = 10.16, p = .003) and more variable (F(1,49) = 6.05, p = .017) response times when signalling their errors on aware error trials relative to young adults. Older adults had significantly slower RT for go-trials (F(1,49) = 8.52, p = .005), as well as for both aware (F(1,49) = 11.56, p = .001) and unaware errors trials (F(1,49) = 9.79, p = .003), relative to young adults. However, for both age-groups, mean error RT on aware error trials was significantly faster than mean go-trial RT (young adults: (t (1,27) = 4.81, p <

.001); older adults (t (1,22) = 3.41, p = .003)), which in turn was faster than mean error RT on unaware error trials (young adults: (t (1,27) = 4.81, p < .001); older adults: (t (1,22) = 3.41, p = .003)). For both groups, there was considerably more within-subject variability (SD) in Mean Awareness RT (young adults: 245.2 ± 66.1; older adults: 262.6 ± 53.8) relative to go-trial RT (young adults: 147.2 ± 46.4; older adults: 182.6 ± 43.3) and error RT on both aware (young adults: 127.1 ± 36.3; older adults: 141.7 ± 44.4; all p < .001) and unaware (young adults: 129.6 ± 66.1; older adults: 165.3 ± 30.9; all p < .001) error trials.

Table 3.1 Performance indices on the EAT for both age groups: mean (SD)

	Young Adults (n= 28)	Older Adults (n= 23)
Accuracy (%)	57.2 (12.5)	57.2 (12.5)
Error awareness (%) *	71.2 (14.1)	63.6 (10.8)
Mean Go-Trial RT (ms)**	527.7 (113.4)	617.4 (103.7)
Mean Error RT (aware errors; ms)**	491.3 (114.9)	594.8 (99.2)
Mean Error RT (unaware errors; ms)**	576.1 (126.9)	691.5 (136.2)
Mean Awareness RT (ms)**	604.4 (102.4)	690.9 (119.1)

** p<.01; * p<.05

ERP data

The grand-average waveforms and spatial topographies for the P100 and N100 for both groups are shown in **Figure 3.1**. First, for the P100, there was a main effect of Age Group (F(1,49) = 4.61, p = .038) on amplitude, but there was no main effect of Error-type (p = .316), and no Age Group X Error-type interaction (p = .571). There was no main effect of either Age Group (p = .44) or Error-type (p = .07) on peak latency, and no Group X Error-type interaction (p = .58). For the N100, there was no main effect of either Age Group (p = .10) or Error-type (p = .29) on peak latency, and no Group X Error-type interaction (p = .78). There was a main effect of Age Group (F(1,48) = 21.27, p < .001) on peak latency, but there was no main effect of Error-type (p = .46), and no Age Group X Error-type interaction (p = .72). Thus, although there were some age-related differences in the latency and amplitude of these early sensory components, neither the P100 nor the N100 differentiated between errors that were detected versus undetected.

The grand-average waveforms and spatial topographies for the ERN for both groups are shown in **Figure 3.2.** There was a strong main effect of Age Group (F(1,49) = 41.95, p <

.001) on the ERN amplitude, but there was no main effect of Error-type (p = .131), and no Age Group X Error-type interaction (p = .99). For peak latency, there was a main effect of Age Group (F(1,37) = 7.24, p = .011), but again there was no main effect of Error-type (p = .787), and no Age Group X Error-type interaction (p = .73). Thus, the ERN was not sensitive to awareness in either group, but older adults had later and substantially attenuated ERNs for both aware and unaware errors, relative to young adults.

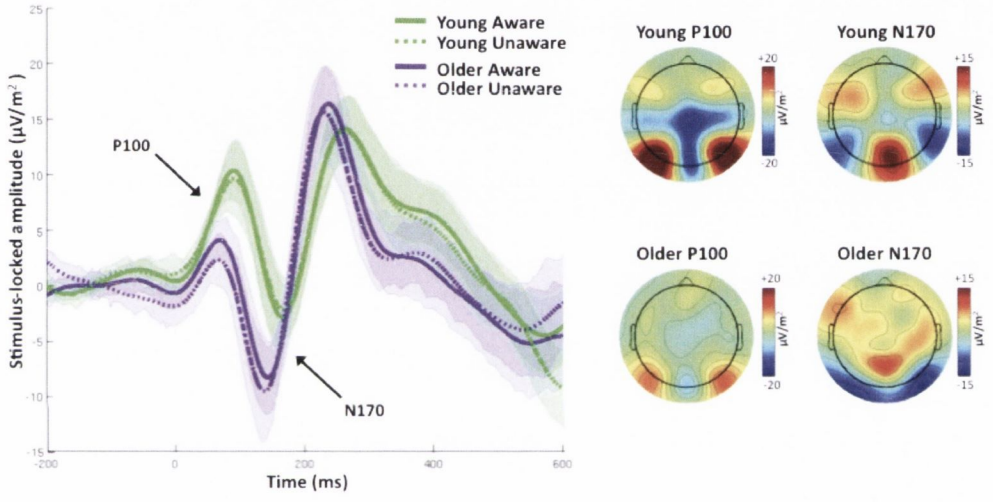

Figure 3.1 Visual-evoked potentials do not predict error awareness. P1 and N1 waveforms of young and older adults aligned to stimulus onset, separately for aware and unaware errors. Spatial topographies show distribution of activity associated with each of the components in young and older adults, collapsed across Error-type. Shaded error bars represent standard error of the mean (s.e.m.)

The grand-average waveforms and spatial topographies for the ERN for both groups are shown in **Figure 3.2.** There was a strong main effect of Age Group (F(1,49) = 41.95, p < .001) on the ERN amplitude, but there was no main effect of Error-type (p = .131), and no Age Group X Error-type interaction (p = .99). For peak latency, there was a main effect of Age Group (F(1,37) = 7.24, p = .011), but again there was no main effect of Error-type (p = .787), and no Age Group X Error-type interaction (p = .73). Thus, the ERN was not sensitive to awareness in either group, but older adults had later and substantially attenuated ERNs for both aware and unaware errors, relative to young adults.

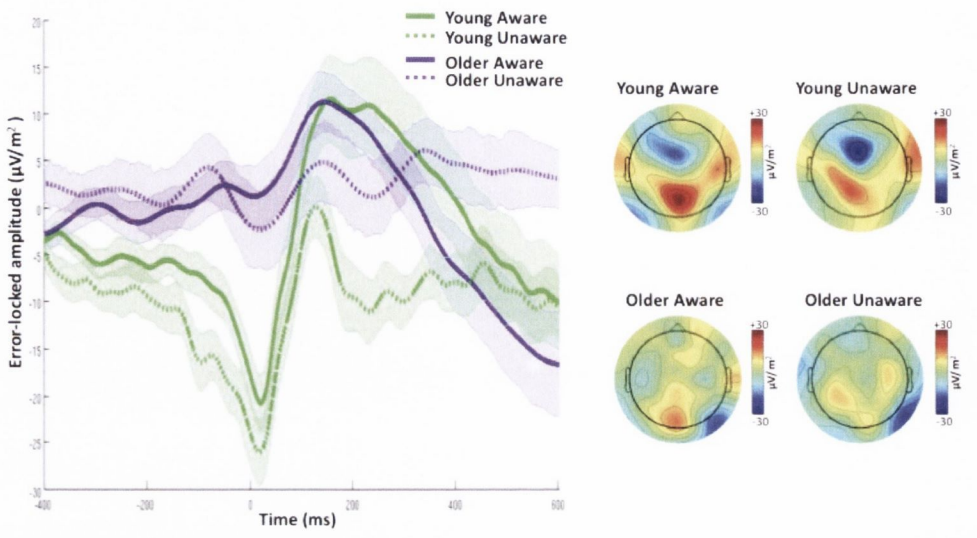

Figure 3.2 The error-related negativity does not predict error awareness. ERN waveforms of young and older adults aligned to erroneous response, separately for aware and unaware errors. There was no difference between the ERN for aware and unaware errors in either group, but older adults had later and smaller ERNs than their young counterparts. Spatial topographies show distribution of associated activity in young and older adults, separately for aware and unaware errors. Shaded error bars = s.e.m.

The grand-average waveforms and spatial topographies for the error-aligned and awareness-aligned Pe for both groups are displayed in **Figure 3.3**. For the error-aligned Pe, there was no group difference in peak latency (p = .28), but older adults had a significantly slower build up rate ($F(1,49) = 4.64$, p = .036), and smaller amplitude ($F(1,49) = 4.23$, p = .045) relative to young adults. For the awareness-aligned Pe, older adults had a significantly later peak latency ($F(1,49) = 6.03$, p = .018) slower build up rate ($F(1,49) = 12.01$, p = .001) and smaller amplitude ($F(1,49) = 14.12$, $p < .001$), relative to young adults.

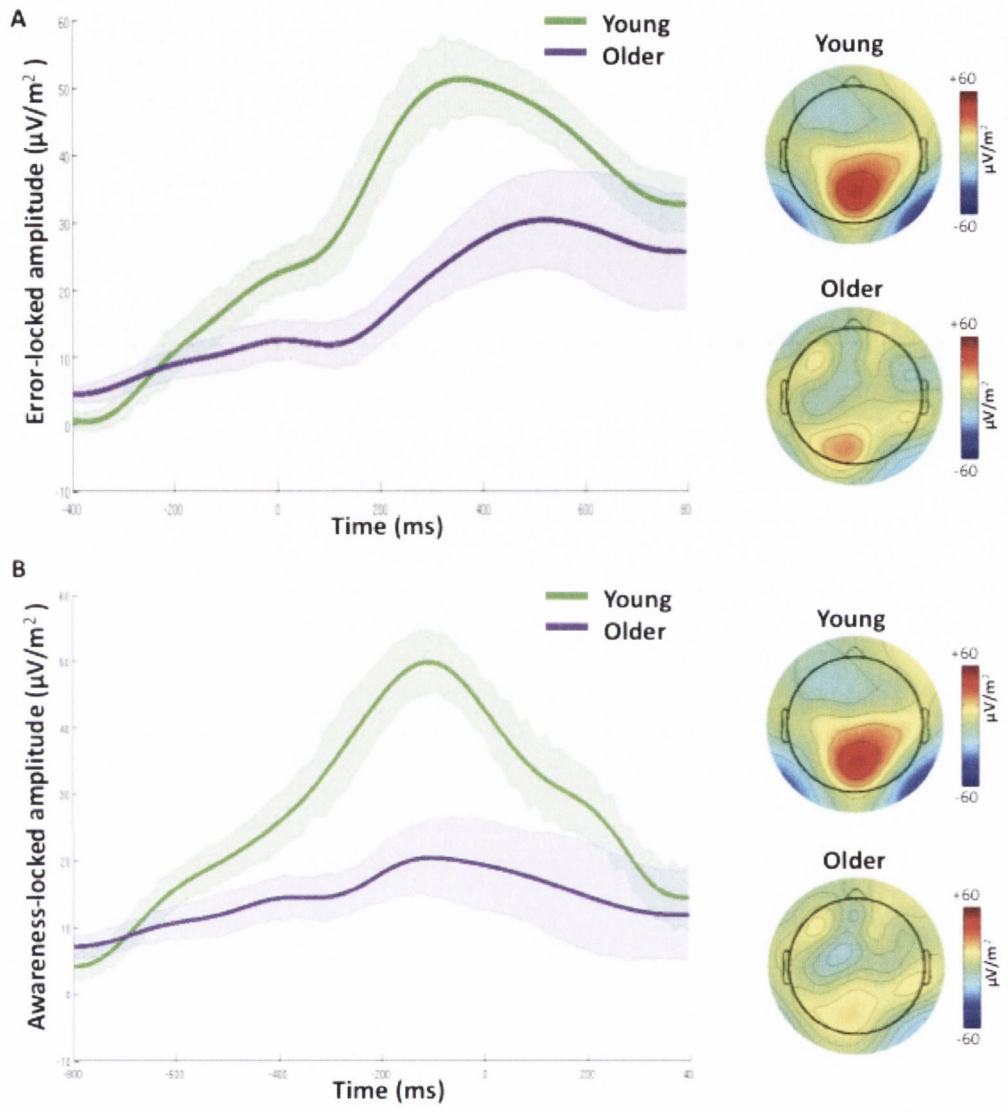

Figure 3.3 The grand-average error positivity for young and older adults. **(A)** Error-aligned Pe waveforms for both age groups. Older adults had a significantly slower build-up rate and smaller amplitude relative to young adults. Spatial topographies show distribution of associated activity in young and older adults. **(B)** Awareness-aligned Pe waveforms for both age groups. Older adults had a significantly slower build-up rate, later peak latency and smaller amplitude relative to young adults. Spatial topographies show distribution of associated activity in young and older adults. Shaded error bars = s.e.m.

A repeated-measures ANOVA revealed a main effect of Age Group ($F(1,48) = 8.46$, $p = .005$), a main effect of Alignment ($F(1,49) = 5.29$, $p = .026$), and an Age Group X Alignment interaction ($F(1,48) = 7.56$, $p = .008$). Paired-samples t-tests indicated that, for

young participants, the difference between the error-aligned and awareness-aligned Pe was non-significant (p = .703), but, for older adults, the amplitude of the awareness-aligned Pe was attenuated relative to the error-aligned Pe $t(22)$= 3.01, p = .007). It was reasoned that this observation might have been attributable to older adults having greater difficulty executing their motor response once they were aware that they had made a mistake. If this were the case, it would potentially introduce a variable time-lag between the peak of the Pe (marking commitment to the error awareness decision) and the awareness press thus leading to an attenuated peak amplitude in the average 'awareness-aligned' waveform. To test this hypothesis, group differences in lag time and lag time variability between single-trial peak latency and Awareness RT were assessed using one-way ANOVA. A non-significant trend towards a group difference in lag time (p = .072) was observed, but most importantly, older adults demonstrated significantly greater lag time variability ($F(1,50) = 4.95$, p = .031). It is therefore plausible that greater jitter in older adults' response execution may have compromised the relationship between the timing of awareness and the grand-average awareness-aligned Pe that has previously been established in young adults (Murphy et al., 2012).

Hence, while the amplitude of the grand-average error-aligned Pe is sensitive to jitter in the timing of awareness (Murphy et al., 2012), the amplitude of the awareness-aligned Pe also appeared to be sensitive to jitter in the preparation and execution of the motor response. To circumvent these constraints and ensure that the reported group differences in the grand-average Pe were not solely attributable to having collapsed the data to the mean, single-trial analyses of the Pe were conducted. Single-trial measures of peak latency, amplitude and build-up rate were extracted and averaged for each participant. One-way ANOVA on the per-subject average single-trial measures revealed that older adults had later peak latencies ($F(1,49) = 12.05$, p = .001), smaller amplitudes ($F(1,49) = 21.78$, $p < .001$), and slower build-up rates ($F(1,49) = 4.19$ p = .046), relative to young adults. Thus, a similar pattern of group differences was also apparent at the single-trial level.

Between-subjects partial correlation analyses were conducted using the per-subject average single-trial measures to examine the relationships between the distinct parameters of the Pe and behavioural measures of error awareness, while controlling for the effect of group. Mean Awareness RT was positively correlated with peak latency (r = .423, p = .002) and negatively correlated with build-up rate (r = -.431, p = .002). Error Awareness was negatively correlated with peak latency (r = -.312, p = .027) and positively correlated with build-up rate (r = .301, p = .034). As expected, given the boundary-crossing effect on decision reports, amplitude was not correlated with either Mean Awareness RT (p = .89) or

Error Awareness (p = .75). Fisher's z tests confirmed that the Pearson's r correlation coefficients for each group were not different for any of the relationships (all $p > .2$) Thus, both young and older adults with steeper build-up rates and early peak latencies of the Pe were also faster at signalling their awareness, and were generally aware of a greater number of the errors they committed.

MF theta

For response-locked MF theta power there was a strong main effect of Age Group ($F(1,98) = 24.61$, $p < .001$), a main effect of Trial-type ($F(1,98) = 22.44$, $p < .001$), but there was no Age Group X Trial-type interaction (p = .289; **Figure 3.4b**). Older adults had significantly reduced MF theta power for Aware errors ($t(1,49) = 3.80$, $p < .001$), Unaware errors ($t(1,49) = 2.71$, $p = .009$) and Standard Go-trials ($t(1,49) = 4.85$, $p < .001$) relative to young adults. However, in both age-groups, Aware error trials were associated with significantly greater MF theta power than Standard Go-trials (young: $t(1,27) = 7.49$, $p < .001$); older: $t(1,22) = 4.71$, $p < .001$)) and Unaware error trials (young: $t(1,27) = 5.66$, $p < .001$); older: $t(1,22) = 2.65$, $p = .015$)). Thus, there was a significant age-related reduction in MF theta power across all trial-types, but older adults' MF theta power nonetheless discriminated Aware error from Unaware error trials in a similar manner to that observed in young adults.

Between-subjects partial correlation analyses, controlling for age group, reinforced the link between MF theta and awareness: Using the per-subject average single trial measure, MF theta power for Aware error trials was negatively related to Mean Awareness RT (r = -.37, $p = .009$) and positively related to Error Awareness ($r = .46$, $p = .001$). Again, Fisher's z test confirmed that the correlation coefficients between MF theta power and Mean Awareness RT (z = -.3, p = 0.76) and Error Awareness (z = 1.17, p = .24) were not significantly different between the two groups. Thus, both young and older adults with a relatively strong MF theta response were faster at signalling error awareness, and generally aware of a greater proportion of the errors they committed.

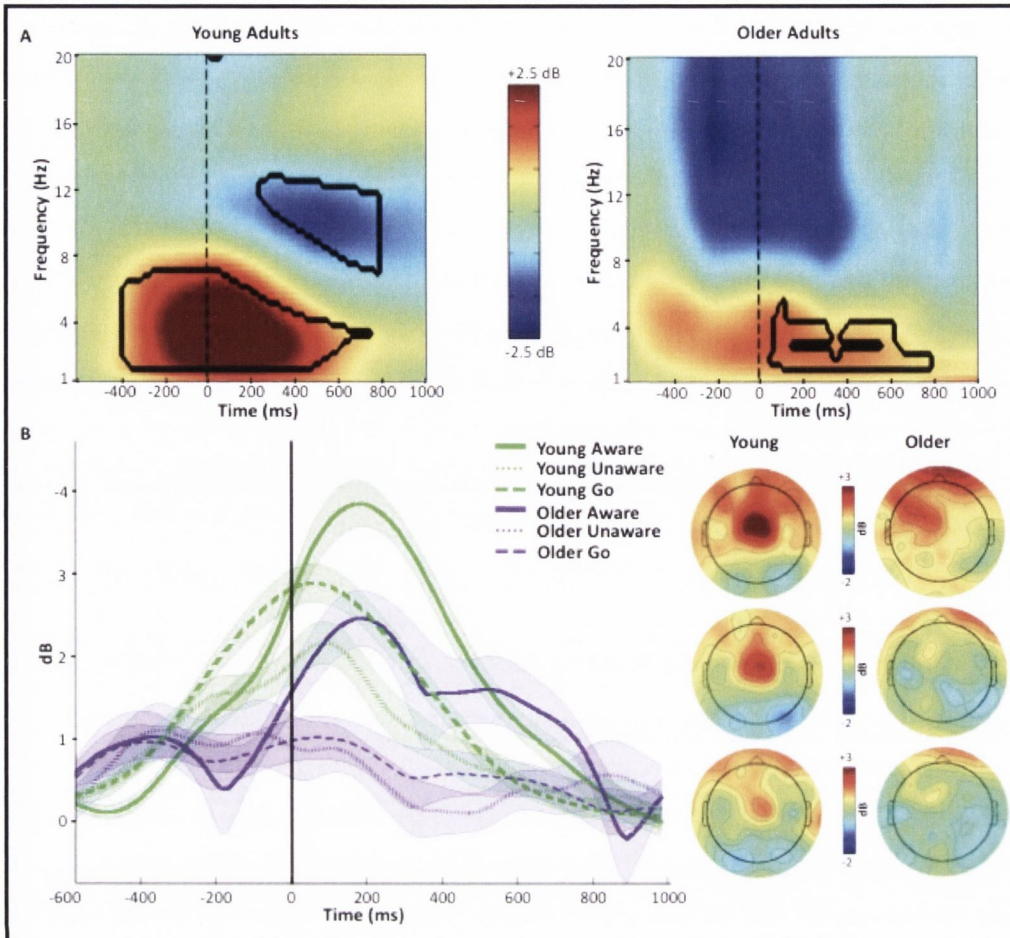

Figure 3.4 Response-locked medial frontal theta in young and older adults. (A) Response-locked time-frequency plots of medial frontal (MF) power, in each age group, averaged across Aware error, Unaware error and Standard Go trials. Black lines encircle regions of significance ($p < 0.01$, paired-samples t-test) relative to a pre-stimulus baseline (300 ms prior to stimulus onset). **(B)** Grand-average temporal evolution of response-locked MF theta (2-7 Hz) waveforms spit by trial-type for each group. MF theta power discriminated Aware from Unaware error trials in both groups, but older adults exhibited a general reduction in MF theta irrespective of trial type. Spatial topographies show distribution of associated activity for Aware error, Unaware error and Standard Go trials in the upper, middle and lower rows, respectively. Shaded error bars = s.e.m.

3.4 Discussion

The recent conceptualisation of the emergence of error awareness as a decision process has offered the field a valuable mechanistic model that makes clear empirically

verifiable predictions regarding both behaviour and the underlying neural implementation. EEG research in turn has identified candidate neural signatures that bear the key characteristics of signals predicted by these models. These signals have exciting potential to benefit research on ageing and clinical disorders because they can be related to specific neural mechanisms and behavioural outcomes. The aim of this chapter was to exploit this knowledge to elucidate the electrophysiological basis of error awareness deficits in healthy older adults. Consistent with the findings in Chapter 2, despite comparable levels of primary task accuracy on the EAT across age groups, older adults exhibited significantly poorer levels of error awareness, relative to young adults. The utilisation of a *speeded*, as opposed to a delayed, error-signalling response in the present study additionally revealed that the emergence of error awareness was both slower and more variable in older relative to young adults. At the electrophysiological level, it was found that VEPs for aware errors were indistinguishable from VEPs for unaware errors in both groups, indicating that older adults' error awareness deficits were not attributable to deficits in sensory processing. On the other hand, analysis of the error-evoked ERPs replicated the finding that error awareness on the EAT task was strongly linked to presence of the Pe, but not the ERN, and group comparisons revealed that both average and single trial measures of older adults' Pe waveforms were characterised by a shallower build-up rate, later peak latency and smaller amplitude compared to young adults. An age-related decrease in MF theta power was also apparent across aware and unaware error trials, as well as go-trials.

In accord with the accumulation-to-bound framework, between-subject correlations revealed significant relationships between Pe build-up and peak latency, and behavioural measures of error awareness in both groups. This accordingly provides reason to be confident that the age-related changes in the morphology of older adults' Pe reflect meaningful changes in the underlying decision process. In the context of the accumulation-to-bound account, the shallower build-up rate and later peak latency of the Pe imply that older adults accumulate internal evidence regarding performance accuracy less efficiently than young adults. On the other hand, the age-related reduction in Pe amplitude points to a lower decision criterion. The lower decision threshold in conjunction with the slower build-up rate indicates that there are opposing effects at play. Namely, a slower build-up rate of the Pe, that delays the decision, juxtaposed with a lower decision threshold which speeds up the commitment to a decision. It is conceivable that, amidst the other age-related changes, the lower amplitude may reflect a compensatory reduction in internal threshold to allow a higher number of errors to cross the boundary for awareness and speed up awareness response times. Given that older adults still exhibit compromised error awareness relative to young adults implies that the apparently lower threshold is not sufficient to fully compensate for

their difficulty with accumulation, but also suggests that the older adults' rates of error awareness may be even worse without it.

The observation of a lower decision criterion in older adults is at odds with modelling work that has been done on first-order perceptual decision-making in older adults, which has instead suggested that age-related changes in perceptual decision-making can by and large be explained by the adoption of a more cautious response mode, consistent with a *higher* decision criterion or a difficulty in adapting their decision criterion in response to changes in speed and accuracy pressure (Forstman et al., 2011; Ratcliff et al., 2006; 2010; Starns & Ratcliff, 2010; Strayer et al., 1987). However, this modelling work was conducted using paradigms that are markedly different from the EAT in that participants must make difficult discriminations about weak or degraded stimuli. Consequently, any uncertainty regarding the accuracy of one's responses arises from the difficulty of perceptual discrimination and not from a failure to adequately monitor performance. The metacognitive judgements required during the EAT are likely to be more multi-faceted and require the integration of multiple sources of internal and external evidence (Ullsperger et al., 2010). This dissimilarity alone highlights how age-related changes in the emergence of error awareness could conceivably be more nuanced than a change in decision criterion setting. Future work should apply sequential sampling models to error detection data of older adults to examine the degree of correspondence between model parameters and the present neural data.

The finding of an age-related reduction in MF theta power across all trial types on the EAT is consistent with the notion that older adults may have performance monitoring deficits that are not unique to error awareness (Anguera et al., 2013; Kolev et al., 2009; Kolev et al, 2005; van de Vijver et al., 2014). At least two studies have also found age-related differences in resting state theta power, and have additionally demonstrated that these changes in resting state theta power were specific to medial frontal areas (Cummins & Finnigan, 2007; van de Vijver et al., 2014). Resting-state MF theta power in older adults also correlates with differences in executive function (Finnigan & Robertson, 2011). Thus, it is likely that the age-related reductions in MF theta in the present study may be related to task independent oscillatory changes in the pMFC, which in turn are possibly related to age-related declines in grey and white matter density (Burzynska et al., 2010; Mann et al., 2011) or glucose related metabolic activity (Pardo et al., 2007) in this brain region.

Despite being generally reduced, older adults' MF theta still conformed to what would be expected of a decision evidence signal for error awareness, exhibiting significantly greater power on aware compared to unaware error trials. The relationship between MF theta

and error awareness was further corroborated by between-subjects correlation analyses indicating that stronger MF theta responses were associated with faster awareness response times and better overall error awareness in both age groups. Collectively, these findings concerning MF theta suggest that at least one source of evidence for an error is less available to older adults, and supports the possibility that older adults' apparent difficulties at the accumulation stage, as reflected by the age-related changes in the Pe, may be attributable to them having weaker evidence available to them from the outset. For instance, O'Connell et al. (2012) have demonstrated that the temporal dynamics of decision signals are highly sensitive to systematic perturbations of decision evidence. Further, a difficulty at the accumulation stage would not be compatible with the modelling work on perceptual decision making in older adults where the majority of studies find no differences in rate of rise of the decision signal (Forstman et al., 2011; Ratcliff et al., 2006; 2010; Starns & Ratcliff, 2010; Strayer et al., 1987). However, as highlighted above, the extent to which such findings generalise the second-order decisions under scrutiny in the present study is open to question. For instance, it should be acknowledged that the ageing process might have different effects on the capacity to accumulate sensory information compared to the accumulation of other sources of evidence that drive the emergence of error awareness, such as the quantity encoded by MF theta, proprioceptive feedback from the erroneous action and interoception of autonomic responses accompanying the error (Yeung et al., 2004; Ullsperger et al., 2010; Wessel et al., 2011). Accordingly, it is not presently possible to exclude the possibility that weaker pMFC generated error evidence and compromised evidence accumulation could have dissociable contributions to older adults error awareness deficits. A previous study has shown that error awareness can be improved via the administration of methylphenidate (Hester et al., 2012). It would be highly interesting for future research to investigate whether such improvements are mediated by changes in error-related MF theta power, Pe dynamics, or a combination of both.

The finding of a significantly reduced ERN in older, relative to young, adults, is consistent with the evidence for a compromised pMFC response as reflected in the age-related reduction in MF theta power. However, unlike MF theta, there was no significant difference between ERN amplitude on aware error compared to unaware error trials. While this finding is consistent with a number of studies (e.g. Niewenhuis et al., 2001; Endrass et al., 2012; Hughes & Yeung, 2011; O'Connell et al., 2009), it is at odds with others (Hewig et al., 2011; Maier et al., 2008; Scheffers & Coles, 2000; Steinhauser & Yeung, 2010; Wessel et al., 2011; Woodman, 2010) that have shown that the ERN is sensitive to error awareness.

A recent study (Shalgi & Deouell, 2012) has highlighted a possible explanation for why the ERN may have been insensitive to awareness in studies such as the present one. Shalgi and Deouell (2012) used a post-decision wagering paradigm that allowed them to dissociate trials in which participants were confident of their performance rating (correct or error) from trials in which they were unsure, and demonstrated that only when ERN measurement was confined to objective errors for which participants were highly confident of their performance rating, the ERN amplitude discriminated aware from unaware errors. This finding was consistent with at least two other studies that have shown that the ERN covaries with subjective confidence in metacognitive decisions (Scheffers & Coles, 2000; Wessel et al., 2011). Accordingly, in studies that have employed error-signalling paradigms such as the present one, a reported error, labelled "Aware" may be accompanied by a relatively low level of awareness, lowering the average amplitude for the "Aware" ERN, while an unreported error, labelled "Unaware" may actually be accompanied by some awareness and therefore add to the average amplitude of the "Unaware" ERN. This highlights the value of paradigms that permit a finer characterisation of the graded nature of awareness. However, rating scales do not afford response time distributions, which are integral to examining error awareness within the accumulation-to-bound framework.

Given that it had previously been established that the traditional approach to measuring the trial-averaged Pe as time-locked to the erroneous response is susceptible to temporal jitter between the point of error commission and the onset of awareness (Murphy et al., 2012), it was deemed important to also examine the dynamics of the Pe aligned to the awareness response. Contrary to expectations, it was found that the amplitude of older adults' awareness-aligned Pe was significantly smaller than the error-aligned Pe. One plausible explanation for this stems from the observation that there was a more variable time lag between the peak latency of the Pe and timing of the awareness response, for older, compared to young, adults. Considering the peak latency of a decision signal (O'Connell & Kelly, 2012; Kelly & O'Connell, 2013) is assumed to mark the point in time at which the decision criterion is reached, this suggests that once sufficient evidence had accumulated to pass the decision criterion, older adults had difficulties in executing their awareness response. Hence, while the trial-averaged error-aligned Pe is sensitive to jitter in the timing of error awareness (Murphy et al., 2012), the amplitude of the trial-averaged awareness-aligned Pe can be comparably affected by jitter in the preparation and execution of the motor response. However, in the present study, the observation of an age-related reduction in amplitude at the single trial level provides evidence against the notion that attenuated amplitude in the trial-averaged Pe can be fully explained by such sources of variability at the post-error stage. The limitations of both trial-averaged methods of measurement nonetheless

speak to need for previous and future investigations of group differences in Pe morphology to verify that any Pe findings that are considered meaningful are also apparent at the single-trial level.

As in previous studies of error awareness (e.g. Endrass et al., 2005; Murphy et al., 2012; O'Connell et al., 2007) it was found that aware error trials, for both young and older adults, were associated with significantly faster response times than correct go-trials, and correct go-trials in turn were faster than response times for unaware errors trials. It has been proposed that this pattern of results is consistent with the idea that aware errors predominantly arise from failures of response inhibition, whereas unaware errors result from lapses of sustained attention (O'Connell et al., 2007; O'Connell et al., 2009; Shalgi et al., 2007). Such a classification would predict that aware error response times should be consistently fast, but on the contrary, the present data indicated that awareness response times of both young and older adults were characterised by substantial between-subject variability and positively-skewed distributions. Thus, for a proportion of aware error trials, awareness did not emerge until quite late. While, at least for older adults, protracted and variable awareness response times may be partially mediated by the motor demands required to execute the awareness response, this substantial variability is not necessarily compatible with the notion that all aware errors are the result of inhibitory failures. Instead, it appears to point to the emergence of error awareness as being a highly variable process, contingent on changeable levels of evidence and rates of evidence accumulation, which in turn are likely related to fluctuations in baseline attentional states.

In summary, the present study constituted the first direct characterisation of the electrophysiological basis of error awareness in healthy older adults. Behavioural measures of error awareness in older adults showed similarly intimate associations with MF theta and the Pe as had previously been documented in young adults (Murphy et al., under review). However, general age-related reductions in MF theta power, as well as in the build-up rate and peak latency of the Pe, suggest that older adults poorer level of overall error awareness is due to weaker pMFC generated error evidence, and/or declines in the ability to accumulate evidence, relating to performance accuracy.

Chapter 4: Transcranial Direct Current Stimulation

4.1 Introduction

Although neuroimaging techniques such as fMRI and EEG are not always strictly correlational (Weber & Thompson-Schill, 2010), the ability to modulate behaviour and neurophysiological processes via brain training and targeted neural stimulation provides critical causal data to inform and substantiate psychological and neuroimaging findings (Zanto, Rubens, Thangavel, & Gazzaley, 2011). Moreover, these approaches also hold additional potential to serve as methods for enhancing cognitive functions in healthy populations (e.g. Marshall, Mölle, Hallschmid, & Born, 2004; Reis, Schambra, Cohen et al., 2009) as well as a range of clinical populations (e.g. Floel, 2014; Fiori, Coccia, Marinelli et al., 2011; Freitas, Mondradón-Llorca, & Pascual-Leone, 2011; Loo, Alonzo, Martin et al., 2012). With respect to the ageing population, cognitive training protocols, in particular, have provided important insights into the capacity of the brain for lifelong learning and adaptive plasticity (Buschkuehl, Jaeggi, & Jonides, 2012; Rebok, Ball, Guey et al., 2014; Willis, Tennstedt, Marsiske et al., 2006; Zelinski, 2009). However, of late, there has been increasing interest in exploring transcranial stimulation techniques that might have the potential to modulate the functioning of neural systems more directly.

One such method is transcranial direct current stimulation (tDCS). tDCS is a noninvasive neurostimulation technique in which a weak electrical current (1 – 2 mA) is passed through electrodes applied to the scalp. The electrodes in this type of stimulation are called the *anode* (positive electrode) and *cathode* (negative electrode), and the current flows into the brain via the anode and out of the brain via the cathode **(Figure 4.1)**. The effect of tDCS on neural activity is still under investigation, but there is a large degree of consensus that anodal stimulation increases the likelihood that a stimulated neuron will produce an action potential by depolarising neuronal membranes, whereas cathodal stimulation

decreases this likelihood by hyperpolarising neuronal membranes (Bindman, Lippold, & Redfearn, 1964; Kuo, Paulus & Nitsche, 2014; Purpura & McMurtry, 1965).

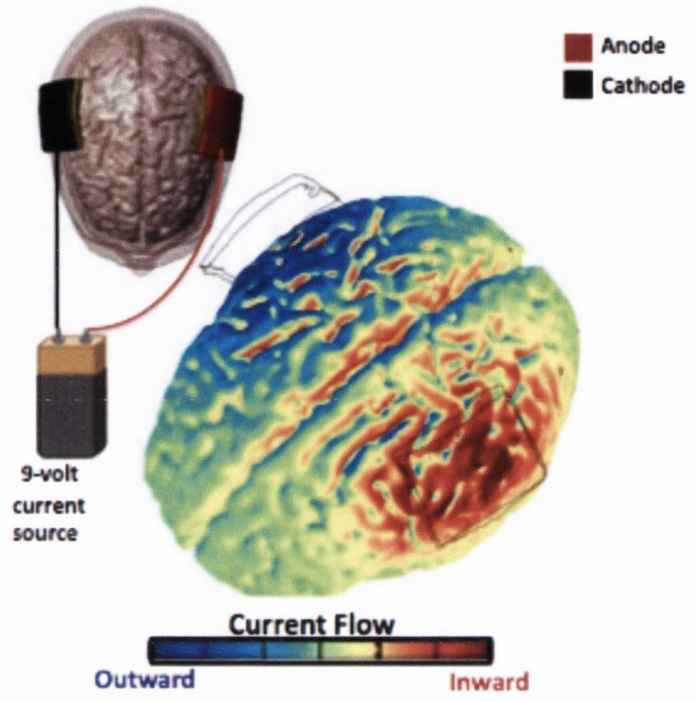

Figure 4.1 Schematic of a tDCS montage and a heat map of the associated current flow. Simplistically, transcranial direct current stimulation is just a battery and two electrodes called the cathode and the anode, which are connected to the negative and positive terminals of the battery, respectively. This schematic is an example of a bilateral tDCS montage, with the cathode placed over the right hemisphere and the anode placed over the left hemisphere. The current flows from the anode to the cathode. Therefore, from the perspective of the brain, the current is entering the brain at the anode and leaving the brain at the cathode, and it is broadly assumed that inwards versus outwards flowing current has opposite effects on the surrounding neurons. Current flowing inwards excites the neurons, whereas, current flowing outwards inhibits the neurons (e.g. Nitsche, Cohen, Wasserman et al., 2008).

Although tDCS has limited spatial focality (Nitsche, Doemkes, Karakoes et al., 2007), in comparison to transcranial magnetic stimulation (TMS), it does have several advantages. Foremost among these is the fact that it is easier to conduct placebo stimulation-controlled studies with tDCS, because, with the exception of slight tingling or itchiness, individuals rarely experience sensations or side effects. Compared to TMS, tDCS is also currently less expensive and much more portable (Gandiga, Hummel, & Cohen, 2006;

Ruffini, Wendling, Merlet et al., 2013). Many of these advantages have led to the increased use of tDCS in clinical and research settings. tDCS has been used to modulate a wide range of perceptual, motor and cognitive functions (Coffman, Clark & Parasuraman, 2014; Kuo & Nitsche, 2012; Nitsche, Antal, Liebetanz, Tergau, & Paulus, 2008), and although large randomised clinical trials are still lacking, it has been identified as showing promise as a tool for treating several psychiatric and neurological conditions including depression (Kuo, Paulus, & Nitsche, 2014; Brunoni, Kemp, Shiozawa et al., 2013), stroke (Floel, 2014), chronic pain (Jensen, Day, & Miro, 2014), and minimally conscious states (Thibaut, Bruno, Ledoux, Demertzi, & Laureys, 2014).

The potential for tDCS to reverse the effects of cognitive ageing in healthy older adults has also been explored in a number of recent studies, with significant tDCS induced changes reported in domains such as working memory (Berryhill & Jones, 2012; Seo, Park, Seo, Kim, Ko, 2011), decision-making (Paulo Sérgio Boggio et al., 2010), object location learning (Flöel et al., 2012), skill acquisition (Zimerman & Hummel, 2010), word retrieval (Meinzer, Lindenberg, Sieg et al., 2014; Ross, McCoy, Coslett, Olson, & Wolk, 2011) and word generation (Meinzer, Lindenberg, Anonenko, Flaisch, & Flöel, 2013). However, to date, the potential impact of tDCS on performance monitoring or error awareness in older age, or in any other population, has yet to be explored.

This chapter does not constitute a comprehensive review of tDCS research, instead, it presents focussed reviews of a select number of topics within the tDCS literature that are of particular relevance to the empirical work presented within Chapter 5 and Chapter 6 of this thesis. The subsequent section provides an overview of what is currently known about the underlying mechanisms of tDCS at the neurochemical, cellular and synaptic level. The third section provides a review of studies that have combined tDCS with fMRI and EEG, and highlights the utility of such combined methodologies for providing valuable insights into the mode of action of tDCS, as well as for identifying and describing functional networks. The fourth section provides an overview of the major methodological considerations and challenges that pertain to research using tDCS. The fifth and final section provides an overall summary and an outline of the objectives for Chapter 5 and Chapter 6.

4.2 Mechanisms of Action

The mechanisms by which tDCS modulates brain functions are not yet fully understood. Existing knowledge of the effects of tDCS on brain functions are summarised

below. Increasing evidence suggests that effects that occur during stimulation are caused by different mechanisms than those occurring after stimulation. Namely, changes in spontaneous neural firing rates and synaptic neuroplasticity are assumed to contribute to intra- and post-stimulation effects, respectively.

Spontaneous neural firing

Unlike other non-invasive brain stimulation techniques such as electroconvulsive therapy and high-intensity TMS, tDCS induces changes in spontaneous neural activity *without* causing action potentials (e.g. Wagner, Fregni, Fecteau et al., 2007). It is unlikely that tDCS directly induces neural firing because according to mathematical models of current flow, the densities of the current that reach the cortex are only between 0.77 and 2 mA/cm^2 (Wagner et al., 2007), which are well below the action potential threshold for neurons (Tehovnik, 1996). Although these current densities may not directly induce action potentials at the time of stimulation, data from animal studies has demonstrated that even small voltage gradients of this magnitude can alter the rate at which neurons fire. Bindman et al. (1964), among others (e.g. Purpura & McMurtry, 1965) have shown that anodal stimulation increases, while cathodal stimulation decreases spontaneous neural firing in *in vivo* animal studies. If stimulation is of sufficient duration, these effects can be long lasting: five to ten minutes of continuous stimulation produced effects that were still apparent after five hours (Bindman et al., 1964).

Several lines of evidence suggest that anodal tDCS shifts the resting membrane potential of neurons toward depolarisation, whereas cathodal tDCS shifts resting membrane potential toward hyperpolarisation. By acquiring intracellular recordings from animals Purpura and McMurtry (1965) were able to demonstrate that anodal stimulation (30-400 $\mu A/mm^2$, for 5 to 40 seconds) causes neurons to depolarise, while cathodal stimulation causes neurons to hyperpolarise. This distinction is supported by evidence that anodal tDCS of the motor cortex increases MEP amplitude, while cathodal stimulation attenuates the MEP (Nitsche & Paulus, 2000; Nitsche & Paulus, 2001; Pellicciari, Brignani, Miniussi, 2013). Similarly, in another study that will be discussed in greater detail below (see *tDCS studies with Neuroimaging*), tDCS over the visual cortex was shown to affect VEPs in a polarity-specific and time-specific manner (Antal, Kincses, Nitsche et al., 2004a).

Further, sodium and calcium concentrations are important determinants of the resting potential of neurons. It has been found that drugs that block sodium channels (e.g. carbamazepine) or calcium channels (e.g. flunarizine) attenuate or eliminate the effect of

anodal stimulation on MEPs both before and after stimulation (Liebetanz, Nitsche, Tergau, & Paulus, 2002; Nitsche, Fricke, Henschke et al., 2003). Interestingly, these same drugs had no effect on the excitability changes associated with cathodal stimulation (Liebetanz et al., 2002; Nitsche et al., 2003). Stagg and Nitsche (2011) have suggested that this might be because cathodal stimulation causes hyperpolarisation of affected neurons and, consequently, inactivation of sodium and calcium channels. Taken together, these findings suggest that tDCS influences neural activity by modulating neuronal membrane potentials.

Synaptic Mechanisms

There is also evidence that tDCS affects neural activity by altering the strength of synaptic transmission. The nature of these synaptic changes are not yet clear, but long-term potentiation (LTP) and long-term depression (LTD) have been identified as candidate mechanisms (Nitsche et al., 2003). LTP refers to a sustained enhancement of synaptic transmission, apparently induced by simultaneous activity of pre- and post-synaptic neurons (Bliss & Collingridge, 1993). LTD, on the other hand, refers to a sustained weakening of synaptic connections (Bliss & Collingridge, 1993). It has been proposed that the polarisation effects of tDCS might modify the threshold for LTP and LTD by facilitating the removal of the magnesium blockade within N-methhy-D-aspartate (NMDA) receptors (e.g. Venkatakrishnan & Sandrini, 2012). Consistent with this hypothesis, it has been found that the after-effects of anodal tDCS are prolonged by the NMDA agonist D-Cycloserine (Nitsche, Jaussi, Liebetanz et al., 2004), reduced by NMDA antagonists such as beta-adrenergic protanol (Nitsche et al., 2004), and completely abolished, irrespective of polarity, by NMDA-receptor antagonist dextromethorphane (Liebetanz et al., 2002). LTP and LTD are also known to depend on protein synthesis (Cooke & Bliss, 2006), and there is evidence to support the notion that tDCS modulates protein synthesis. For instance, it has been found that when pharmacological agents that inhibit protein synthesis, such as 8-azaguinine, are ingested during tDCS, they reduce the after-effects of the stimulation. The same pharmaceuticals produce no significant effect when ingested once after-effects have already appeared (Gartside, 1968). These findings indicate that NMDA and protein synthesis are affected by tDCS and accordingly also support the hypothesis that LTP and LTD processes, may play a role in the prolonged effects of tDCS.

Neurotransmitters

Studies using magnetic resonance spectroscopy (MRS; Stagg, Best, Stephenson et al., 2009; Stagg & Nitsche 2011) and drug studies targeting specific neurotransmitter receptors (e.g. Liebetanz et al., 2002; Nitsche et al., 2004) have provided further evidence that tDCS modulates synaptic activity. For instance, using MRS, Stagg et al. (2009) showed that anodal stimulation leads to a specific decrease in GABA concentration, whereas cathodal stimulation leads to a decrease in glutamate. These findings are of particular interest given that GABA and glutamate are known as the most important inhibitory and excitatory neurotransmitters in the central nervous system, respectively (Ziemann, 2011). In a subsequent study by the same group (Stagg et al., 2011), which involved fMRI in addition to MRS, it was found that the GABA decreases induced by anodal stimulation over the primary motor cortex (M1) correlated with improvements in motor learning and changes in BOLD signal within M1. These findings are compatible with a number of other reports of anodal stimulation inhibiting neurotransmission by GABA and cathodal stimulation inhibiting neurotransmission by glutamate (Kim, Stephenson, Morris, Jackson, 2014; Nitsche, Liebetanz, Schlitterlau et al., 2004). Such modulations of synaptic processes demonstrate the potential of tDCS to influence synaptic plasticity (Stagg & Nitsche, 2011), and indicate that GABA and glutamate play a role in the effects of tDCS on brain function.

A number of other neurotransmitter systems have been implicated in the effects of tDCS. A serotonin reuptake inhibitor (citalopram) has been shown to reverse the inhibitory effect of cathodal stimulation, and to enhance and elongate gains in excitability following anodal stimulation. It has also been shown that genetic polymorphisms (5-HTTPLR) linked to the functioning of the serotonergic system predict the outcomes of tDCS interventions in patients with major depressive disorders (Brunoni et al., 2013). These findings thus suggest an effect of tDCS on the serotonergic system, as well as highlighting the importance of genetic factors in mediating inter-individual responsiveness to tDCS. The cholinergic system may also play a role in the effects of tDCS. Kuo et al. (Kuo, Grosch, Fregni, Paulus, & Nitsche, 2007) have reported that acetylcholine inhibitors eliminate the typical increase in excitability elicited by anodal stimulation, and diminish the effect of cathodal stimulation. This is compatible with the observation that the administration of nicotine, an acetylcholine agonist, abolishes the post-stimulation effects of stimulation (Thirugnanasambandam, Grundey, Adam et al., 2010). Lastly, a role for the dopaminergic system has been highlighted by studies showing that the administration of L-dopa can reverse the typical increase in excitability induced by anodal stimulation, and elongate the inhibitory effects following cathodal stimulation (Kuo, Paulus, & Nitsche, 2008, Monte-Silva, Liebetanz, Grundey, Paulus, & Nitsche, 2010). Thus, tDCS can modulate GABA, glutamate, serotonin,

acetylcholine and dopamine systems. These neurotransmitter systems are known to affect synaptic plasticity via modification of the excitability of neurons, enhancement of signal-to-noise ratio of cortical responses, and modulation of the threshold for activity-dependent synaptic modifications (Gu, 2002). Accordingly, modulations of these of neurotransmitter systems via tDCS likely affect plasticity processes.

4.3 tDCS Studies with Neuroimaging

As evident from a few of the studies already mentioned above, pairing tDCS with neuroimaging methods can provide valuable information on tDCS mechanisms of action. In this subsection more studies that have combined the use of tDCS with fMRI and EEG methods are evaluated, and it is highlighted how in addition to providing important insights on the mechanisms underlying tDCS, these studies represent a powerful approach for identifying and describing functional networks, and have the potential to provide an especially compelling case for the causal role of brain regions in particular functions.

Functional magnetic resonance imaging

In one of the first studies that combined tDCS with fMRI, Baudewig et al. assessed the effects of cathodal stimulation applied over left M1 on the BOLD signal while participants performed a sequential finger opposition task (Baudewig, Nitsche, Paulus, & Frahm, 2001). They showed that the administration of 1mA of cathodal tDCS for five minutes resulted in a 38% decrease in the mean number of activated voxels, and these reductions were even more prominent in the supplementary motor area (SMA) and other functionally related areas, than in left M1. Similarly distributed activation changes were observed in another study that examined the effects of both anodal and cathodal tDCS over left M1 while participants performed a visually cued serial reaction time task. Compared to the sham condition, anodal stimulation led to activation increases in both left M1 and the SMA, while cathodal stimulation produced a relative increase in the contralateral M1 and dorsal premotor area, as well as increased functional connectivity between these areas and the stimulated left M1 (Stagg et al., 2009). In related work, a graph theory analysis of resting-state fMRI data found that anodal tDCS over left M1 coupled with cathodal tDCS over the contralateral frontopolar cortex resulted in a global *decrease* in the long-distance

functional coupling of the left M1 with the rest of the brain (Polanía, Paulus, Antal, & Nitsche, 2011). The authors of this latter study hypothesised that the local increase of spontaneous activity due to anodal tDCS over left M1 may have decreased the neuronal signal-to-noise ratio and consequently decreased the synchronisation with other functionally related brain regions.

Distant and remote effects of tDCS have also been observed in studies that have stimulated non-motor areas. A recent investigation of the dynamic interactions within and across resting-state networks before and after the application of tDCS over the left and right dlPFC revealed a redistribution of activity across resting-state networks (Pena-Gomez et al., 2012). Anodal tDCS resulted in site-specific increases in *synchronous* activity between lateral frontal and parietal areas and *asynchronous* activity in medial prefrontal and medial posterior areas, which comprise the default-mode network (e.g. Raichle & Snyder, 2007). Holland et al. (Holland, Leff, Josephs et al., 2011) found that anodal stimulation over left inferior frontal cortex of stroke patients led to increased activity in both left dlPFC and Broca's area, and further demonstrated that there was a positive correlation between the tDCS-induced activation increases in Broca's area and improvements in performance of a picture naming task.

Recently, Meinzer et al. (2013) have provided some of the first evidence that tDCS may mitigate age-related changes in both behavioural performance and BOLD activity. Having previously established that age-related declines in performance on a semantic word generation task were associated with hyperactivity in bilateral frontal areas (Meinzer, Flaisch, Seeds et al., 2009), the authors sought to determine whether anodal tDCS (1mA, 35cm^2 electrode, 20 minutes) applied over left ventral inferior frontal gyrus (IFG) would modulate semantic word generation and the accompanying BOLD signals in healthy older adults. This anodal tDCS protocol resulted in a number of changes. First, it temporarily enhanced older adults' performance on the semantic word generation task to a level that was comparable with younger controls. Second, it reversed the increment of activity observed in bilateral ventral IFG and right medial frontal gyrus in older relative to younger participants. Anodal tDCS induced reductions in task-related activity in areas outside the a priori targeted regions, the precuneus and anterior cingulate gyrus, which have also been shown to be hyperactive in older adults (Milham, Erickson, Banich et al., 2002; Meinzer, Seeds, Flaisch et al., 2012; Persson, Lustig, Nelson, Reuter-Lorenz, 2007). Third, anodal tDCS induced large-scale network changes as evinced by alterations in functional connectivity during resting state. Specifically, the hypoconnectivity in posterior regions and hyperconnectivity in fronto-temporal regions observed in older adults was partially reversed by anodal tDCS.

These findings were the first to suggest that anodal tDCS not only ameliorates age-related behavioural impairments, but also induces changes in neural activity and connectivity, that reflect more "youth-like" processing (Meinzer et al., 2013).

Taken together, these studies indicate that tDCS can result in polarity-specific modulations of neural activity underlying the electrodes, but also in functional connectivity across distal brain regions.

Electroencephalography

Studies combining tDCS with EEG have provided equally important insights on the brain areas that are directly or indirectly affected by tDCS. As already highlighted in Chapter 1 and Chapter 3 the analysis of ERPs can provide information about the brain regions involved in various types of encoding processes, and in particular the precise time course of such processes. As such, comparing the amplitude and latency of ERPs across baseline and tDCS conditions may provide important information regarding the effects of tDCS on neural activity. Similarly, investigating tDCS effects on EEG oscillatory activity can help elucidate the influence of tDCS on physiological and psychological processes associated with particular frequency bands, as well as communication between different cortical areas.

Significant technical problems can arise during the acquisition of EEG data concurrent to tDCS. Accordingly, the vast majority of combined EEG-tDCS studies have adopted what is known as the "offline" approach to evaluate the short- to long-term after-effects of tDCS on EEG measures while subjects perform a task or while at rest (Miniussi, Brignani, & Pellicciari, 2012). However, as will be discussed below, the "online" approach of evaluating real-time changes during tDCS delivery is becoming increasingly more common.

Offline approach. In a study that was briefly mentioned above, Antal et al. (2004a) evaluated the capacity for tDCS to affect VEPs in a polarity-dependent manner during the presentation of visual stimuli. VEPs were recorded immediately after, and 10, 20, and 30 minutes after the delivery of 5, 10, or 15 minutes of anodal or cathodal stimulation (1mA, 35cm^2) over the primary visual cortex (V1). The differential influence of three distinct electrode montages (Cz-Oz, O1-O2, and Oz-mastoid, according to the 10–20 international system for electroencephalogram electrode placement), were also examined. It was found that anodal and cathodal tDCS increased and decreased, respectively, the amplitude of an early occipital component (N70). Differences in the size and duration of the effect were also reported, with a stronger and faster effect for cathodal relative to anodal tDCS, and longer

stimulation periods were found to be more effective in modulating the VEPs. A trend toward an increase in the amplitude of the P100 component was also observed, but only after cathodal stimulation. These differences were only significant for the Cz-Oz electrode montage, indicating that stimulation site is an important determinant of tDCS-induced modulations. Thus, the measurement of VEPs and the study of current polarity-specific effects in this study allowed the authors to infer the magnitude and direction of the visual cortical excitability changes induced by tDCS.

Accornero et al. (Accornero, Li, Voti, La Riccia, & Gregori, 2007) employed a similar approach but used a non-cephalic electrode (the posterior neck base). Following 3 or 10 minutes of cathodal stimulation (1mA, 40cm^2 electrode) over V1, an increase in the amplitude of the P100 component was observed, whereas anodal stimulation resulted in a decrease in amplitude of the same component. These findings are somewhat discrepant from the results reported by Antal et al. (2004a) who only observed a trend towards an effect on the P100 following cathodal tDCS and no effect following anodal tDCS. This discrepancy has several plausible causes, including differences in the electrode size and location of the return electrode (and accordingly the intensity, location and direction of the current), as well as differences in the task stimuli used to evoke the VEPs. Together, these studies suggest that tDCS directly modulates the activity of V1 neurons in a polarity dependent manner, and several technical parameters are important in determining the efficacy of the stimulation.

Zaehle et al. (Zaehle, Beretta, Jancke, Herrmann, & Sandman, 2011a) sought to establish if tDCS over the auditory cortex also affects auditory evoked potentials (AEPs). These authors measured the AEPs (P50 and N1) following anodal and cathodal tDCS (1.25 mA, 35cm^2 electrode, 11 minutes) applied over the temporal (T7) and temporoparietal (TP5) cortices. Anodal tDCS over the temporal cortex increased the P50 amplitude, whereas cathodal tDCS over temporoparietal cortex gave rise to an increase in N1 amplitude. These findings are consistent with previous work indicating a polarity-specific effect on neural activity. Zaehle et al. (2011a) proposed that opposing effects of tDCS on P50 and N1 components might reflect differential effects of tDCS on different types of neurons within the auditory cortex.

Kirimota et al. (Kirimoto, Ogata, Onishi, et al., 2011) applied anodal and cathodal tDCS (1mA, 9cm^2 or 17cm^2 electrodes, 15 minutes) over the dorsal premotor cortex. Somatosensory evoked potentials (SEPs) and MEPs were recorded before and after stimulation. Anodal tDCS, applied with the larger electrode, resulted in an increase in the amplitudes of SEP components (N20 and P25), whereas cathodal tDCS had the opposite effect. The opposite pattern of results was observed for the MEPs: anodal and cathodal tDCS

resulted in a decrease and increase, respectively, in the amplitudes of the MEP components. The smaller electrode size did not influence the SEPs or MEPs, irrespective of polarity. Thus tDCS over the dorsal premotor cortex had opposite effects on primary motor and somatosensory areas. These findings suggest that the dorsal premotor region has an inhibitory input to M1 and an excitatory input to the somatosensory cortex (Kirimoto et al., 2011).

A number of studies have also investigated the effect of tDCS on oscillatory activity when applied over motor, visual and prefrontal cortices. Ardolino et al. (Ardolino, Bossi, Barbieri, & Priori, 2005) were among the first to study the modulations in oscillatory activity induced by tDCS applied over the motor cortex. Cathodal (1.5 mA, 35 cm^2 electrode, 10 minutes) and sham tDCS were administered over M1 while participants were in a resting state. Analyses of the EEG data before and after tDCS revealed increases in the power of delta (2-4Hz) and theta (4-7Hz) frequency bands after cathodal stimulation that were not apparent following sham tDCS. No effects of stimulation were observed in alpha, beta or gamma (>8Hz) frequency bands.

In another study by Antal et al. (Antal, Varga, Kincses et al., 2004b) anodal and cathodal stimulation (1mA, 35cm^2 electrode, 10 minutes) was applied over Oz with the return electrode positioned over Cz. EEG was recorded during the presentation of visual stimuli prior to stimulation and at 0, 10, 20, and 30 minutes after the stimulation had terminated. The authors observed an attenuation of power within beta (15-31Hz) and gamma (31-65Hz) frequency bands after cathodal tDCS, whereas no changes were found after anodal tDCS. The effects induced by cathodal stimulation were evident immediately after, and at both 10 and 20 minutes after the end of stimulation. These findings are consistent with the previously discussed findings of the same research group (Antal et al., 2004a), and with the notion that power of high frequencies is correlated with performance in visual tasks (Siegel, Donner, Oostenveld et al., 2007).

Zaehle et al. (Zaehle, Sandmann, Thorne, Jänke, & Herrmann, 2011b) were among the first to employ EEG to examine the neural mechanisms through which tDCS affects cognitive performance. The authors examined the effects of anodal and cathodal stimulation (1mA, 35 cm^2 electrode, 15 minutes) with the active electrode placed over left dlPFC (F3) and with the return electrode placed over the left mastoid. tDCS was applied while the participants were in a resting-state, whereas the EEG was acquired during the performance of a verbal working memory task after the stimulation had terminated. Consistent with previous behavioural findings (for a review see Brunoni & Vanderhasselt, 2014) they found that anodal tDCS led to an increase in working memory performance, while cathodal tDCS

interfered with performance, relative to sham stimulation. They also identified that these behavioural effects were accompanied by amplification of oscillatory activity in the theta frequency band and attenuation of activity in the alpha bands. In the context of working memory paradigms, increased power in the theta band has been associated with memory encoding and retrieval (Jensen & Tesche, 2002), while increases in alpha power are assumed to reflect a state of low cortical excitability, conducive to inhibiting non-task relevant information (Klimesch, Doppelmayr, Röhm et al., 2000).

Keeser et al. (Keeser, Padberg, Reisinger et al., 2011) also examined the effects of tDCS on working memory and associated oscillatory activity. However, they only applied anodal (2mA, 35cm^2 electrode, 20 minutes) and sham tDCS, with the active electrode over left dlPFC (F3) and the return electrode positioned above the contralateral supraorbital region. Following tDCS, which was applied while the participants were at rest, EEG was acquired during an eyes closed resting-state followed by a working memory (the n-back) task. Using spectral power analysis and standardised low-resolution tomography (sLORETA), the authors found that anodal tDCS resulted in a reduction in the mean current densities for the delta band in the left subgenual PFC, in the anterior cingulate, and in the left medial frontal gyrus. This effect on neural activity was accompanied by a positive impact on error rate, accuracy and reaction time and increases in the amplitudes of the P200 and P300 ERP components. These results thus suggested that anodal tDCS of left dlPFC and/or cathodal tDCS (i.e. through the 'return' electrode) of the contralateral supraorbital region may modulate electrical activity in the PFC *and* ACC, in addition to improving working memory performance. These studies by Zaehle et al. (2011b) and Keeser et al (2011) were among the first to demonstrate an association between stimulation induced EEG changes and functionally relevant changes in cognitive functions.

Online approach. The above studies demonstrate the advantages of combining EEG and tDCS offline, but an increasing number of authors are recognising the value of the online approach for providing real-time information on the neurophysiological effects that are directly associated with tDCS (Accornero et al., 2007; Romero Lauro, Rosanova, Mattavelli et al., 2014; Mangia, Pirini, & Cappello, 2014; Miniussi, Brignani, & Pellicciari, 2012; Schestatsky, Morales-Quezada, & Fregni, 2013; Soekadar, Witkowski, Cossio et al., 2014; Strigaro, Mayer, Chen, Cantello, & Rothwell, 2014; Wirth, Rahman, Kuenecke et al., 2011). Owing to the significant technical problems that can be encountered during EEG-tDCS co-registration only a limited number of studies have successfully applied this approach (Miniussi et al., 2012). The main reasons EEG recording during tDCS may be technically challenging can be summarised as follows: 1) Most EEG systems use wet electrodes to

enhance the conduction between the electrodes and the scalp. Likewise, the administration of tDCS also requires good conduction, typically facilitated by saline solution, electrolyte gels or pastes. If the conductive agents for the EEG electrodes and the tDCS electrodes are in direct contact, the stimulation currents will saturate the EEG amplifier, and accordingly interfere with the acquisition of electrophysiological recordings (Soekadar et al., 2014); 2) Even if the respective conductive agents are not touching, tDCS can introduce an electrical field that can saturate EEG amplifiers. However, as pointed out by Miniussi et al. (2012), this should typically only be a problem at the beginning of stimulation due to the initiation of the current inducing charges in the electrodes, amplifiers, and skin.

In theory, the technical challenges of acquiring EEG concurrent to tDCS can be overcome by ensuring that the conductive agents used for the EEG electrodes and the tDCS electrodes do not bridge and waiting several seconds for the EEG signal to recover from the onset of the tDCS current. By heeding these factors a number of authors have successfully achieved EEG-tDCS co-registration (Accornero et al., 2007; Accornero, Capozza, Pieroni et al., 2014; Romero Lauro et al., 2014; Mangia et al., 2014; Schestatsky et al., 2013; Soekadar et al., 2014; Strigaro et al., 2014; Wirth et al., 2011).

For instance, in the language domain, Wirth et al., (2011) evaluated the electrophysiological underpinnings of the behavioural effects induced by anodal stimulation (1.5 mA, 35 cm^2 electrode, 37 minutes) applied over left dlPFC (F3) during an overt picture naming task. The return electrode, the cathode, was affixed to the contralateral shoulder. Both behavioural and EEG variables were examined during and after stimulation. Their main findings were an online enhancement of an ERP component associated with the functional integrity of the language system, and an offline reduction in delta activity. Both these EEG findings are consistent with the notion that anodal tDCS induced an excitatory effect on frontally mediated neural processes and related language functions. However, the findings also highlight how meaningful changes in electrophysiological variables may be overlooked when researchers only investigate the offline effects of tDCS on the EEG.

It is clear from the research reviewed within this section that pairing tDCS with neuroimaging methods represents a powerful approach for gaining sophisticated insights into the mode of action of tDCS, as well as for identifying and describing functional networks. It accordingly becomes possible to test hypotheses regarding causal interactions between brain regions in health and disease. A peculiarity that pertains to much of the research discussed in this section, as well as the preceding section, concerns how highly similar electrode montages can give rise to such diversified effects on behaviour and neurophysiology. In a recent review, Miniussi et al. (Miniussi, Harris, & Ruzzoli, 2013) have provided some

explanations for why this would appear to be the case. Primarily, they point out how due to the fact that the currents involved in tDCS are not sufficient to induce depolarisation, it will only increase the firing of neurons that are already near threshold, meaning that neurons that are not engaged by a given task are less likely to discharge. Accordingly, tDCS related effects are likely to hinge critically on the state of the networks at a given moment. Consistent with this, several studies that have indicated that for the application of tDCS to be effective in altering motor performance and learning in both healthy and clinical populations, it needs to be administered during task performance (Dockery, Hueckel-Weng, Birbaumer, & Plewnia, 2009; Galea & Celnik, 2009; Hunter, Sacco, Nitsche, & Turner, 2009; Nitsche et al., 2003; Nitsche et al., 2007). Minussi et al. (2012) additionally propose that the tDCS-induced polarisation of neurons in combination with ongoing synaptic input due to task execution can be conceptualised as synaptic co-activation. This conceptualisation, being reminiscent of Hebbian-like plasticity mechanisms, provides a plausible account of how tDCS may be capable of inducing enduring neural network changes.

4.4 Methodological Considerations

As is evident from the studies discussed above, the tDCS literature is rife with inconsistencies in stimulation parameters and study designs, which can limit the interpretation of results, as well as the scope for synthesising findings from different research groups. A number of these factors are discussed below.

Current density

The capacity for tDCS to modulate cortical activity depends on the quotient of current strength and electrode size, i.e. the current density, which dictates the strength of the induced electrical field (Nitsche et al., 2008). Increasing the current density increases the depth of penetration of the electrical field (Sehm, Hoff, Gundlach et al., 2013), but it is generally not recommended to increase the current density beyond a certain threshold as it can induce cutaneous pain sensation in the participant (Nitsche et al., 2008). Further, it has been shown that 2 mA may not lead to stronger effects than 1 mA on working memory performance and associated neural signatures, but instead can actually reveal weaker or qualitatively different changes (Hoy, Emonson, Arnold, Thomson, & Daskalakis, 2013). Yet, on the other hand, it has also been shown that in some instances it is necessary to apply

currents of greater strength to observe an effect of tDCS (Fregni, Boggio, Nitsche et al., 2005; Iyer, Mattu, Grafman et al., 2005). For example, Iyer et al. (2005) found that although a current strength of 2mA successfully produced an improvement in verbal fluency, 1mA did not. Thus, current density does not necessarily have a linear relationship with neural or behavioural modulation.

Specificity of stimulation

The regional specificity of tDCS effects are primarily limited by the size of the stimulating electrodes (Gandiga, Hummel, & Cohen, 2006). The smallest electrode size used in tDCS research is approximately 2.5 x 2.5 cm. The advantage of the relatively large electrodes is that it ensures that the technique is safe and painless (Iyer et al., 2005; Poreisz et al., 2007). However, the large electrodes are also associated with low spatial resolution (Wagner et al., 2007). Findings from studies in which fMRI has been used to measure tDCS induced changes in brain activation (see *tDCS studies with neuroimaging*, this chapter), as well as from models of tDCS current flow (e.g. Bai, Loo, & Dokos, 2013; Russell, Goodman, Pierson et al., 2013; Wagner, Rampersad, Aydin et al., 2014), indicate that tDCS can alter processing across distant cortical and sub-cortical brain regions. Hence, although neural changes induced by tDCS are more concentrated around the regions of cortex closest the tDCS electrodes (Wagner et al., 2014), broader networks of functionally connected neural substrates may also be affected (e.g. Polanía et al., 2011). Accordingly, in the absence of neural evidence, researchers should be cautious about linking a specific process to a small region of the cortex on the basis of tDCS induced changes in processing or behaviour.

It is also important that studies account for the fact that the return electrode is not physiologically inert. It is indeed possible that any observed effects of tDCS on behaviour are attributable to stimulation under the return electrode, or an interaction between the site targeted for 'active' stimulation and the site chose for the 'return' electrode. This possibility can be excluded by incorporating appropriate control experiments, or mitigated by using a relatively large return electrode to reduce the current density (Garin, Gilain, Van Damme et al., 2011). An alternative way to avoid this ambiguity is to choose an extracephalic location for the positioning of the return electrode. However, the results achieved by these protocols might differ from those that position the return electrode over a cephalic region (Accornero et al., 2007; Antal, Kincses et al., 2004; Nitche & Paulus, 2000). This may be attributable to associated differences in the paths travelled by the current, or to the fact that the magnitude and duration of tDCS-induced after-effects are known to correlate negatively with the inter-

electrode distance (Moliadze, Paulus, & Antal, 2010). Thus, positioning the return electrode over an extracephalic region may be disadvantageous in some instances.

Similarly, designs in which a bilateral electrode montage is employed make it challenging to apportion effects specifically to the anode or the cathode, and will accordingly constrain the inferences that can be made about the underlying neural mechanisms. This limitation of bilateral montages can often be overcome, however, by subsequently examining how the effects compare when the locations of the anode and cathode are flipped (e.g. Sparing, Thimm, Hesse, Karbe, & Finke, 2009).

Duration of stimulation

The duration for which stimulation is administered is one of the most important determinants of the lasting effects of tDCS (Nitsche, Antal, Liebetanz et al., 2008; Nitsche, Nitsche, Klein et al., 2003; Nitsche & Paulus, 2000; Nitsche & Paulus, 2001). Nitsche and Paulus (2000) found that brief stimulation of M1 had short-lasting effects on motor cortex excitability, which did not outlast the stimulation period itself. Whereas, researchers from the same group have also shown that effects on motor cortical excitability induced by 9 minutes of stimulation can last up to half an hour, and the effect of 11 minutes of stimulation can last for an hour (Nitsche et al., 2008; Nitsche et al., 2003; Nitsche & Paulus, 2001).

Baseline measures

Many tDCS studies include a 'sham' stimulation condition as a baseline against which to compare the impact of active tDCS. Usually, a sham condition will constitute a substantially reduced current flow, either in terms of intensity or duration, compared to the active tDCS condition, but still enough to induce sensations that mimic those perceived during active tDCS. Although it is broadly assumed that participants cannot discriminate between sham and active tDCS (Russo, Wallace, Fitzgerald, & Cooper, 2013), concerns regarding the validity of this assumption have been mooted (Horvath, Carter, & Forte, 2014; O'Connell, Cossar, Marston et al., 2012). Even when participants cannot consciously distinguish sham from active tDCS, there may nonetheless be differences in other relevant factors such as arousal (Horvath et al., 2014). Studies should therefore endeavour to incorporate appropriate control conditions into study designs. Such control conditions could involve conducting a control experiment in which an alternative electrode montage that does not target the region of interest is examined, or comparing anodal and cathodal tDCS effects. Administering a questionnaire to investigate differences in perceptions after each

experimental condition is another means by which potential placebo and/or somatosensory effects due to tDCS can be controlled for.

Factors affecting data variability

The reliability of the findings from tDCS studies can vary both from session to session within individuals, and across participants (Horvath et al., 2014). Reasons for within-subject variability include individual modulating factors such as the consumption of neuro-affective substances like nicotine and caffeine (Thirugnanasambandam et al., 2010), and fluctuations that occur over time. For instance, time of day, is known to affect motor cortex excitability and plasticity, as measured by TMS (Sale, Ridding, & Nordstrom, 2007).

Mathematical models of current flow indicate that some inter-individual differences in responsiveness to tDCS are undoubtedly due to differences in current flow between individuals. Head size and shape, as well as the thickness and density of an individual's skin, skull, cerebral spinal fluid, grey matter and white matter all have a role to play in the pathway and distribution of the current (Russell, Goodman, Pierson et al., 2013). These individual differences may be further exaggerated in cases where there are abnormalities in the brain tissues, such as brain lesions, that could alter conductivity (Russell et al., 2013).

Inter-individuals differences in tDCS induced changes may also be attributable to age and years of education (Berryhill & Jones), differences in neurotransmitter efficiencies (Brunoni et al., 2013; Ridding & Ziemann, 2010), genetic polymorphisms (Ridding & Ziemann, 2010), as well as hormone levels (cf. Sale et al., 2007). For instance, the influence of ovarian hormone changes on task performance and responsiveness to stimulation has been demonstrated in many TMS studies (Inghilleri, Conte, Curra et al., 2004; Sale et al., 2007; Smith, Adams, Schmidt, Rubinow, & Wasserman, 2002; Smith, Keel, Greenberg et al., 1999). Specifically, these studies have shown that that the cortical excitability of male and female participants is only similar during the follicular phase of the menstrual cycle when progesterone levels are low and oestrogen levels are high (Inghilleri et al., 2004). Consistent with this, tDCS studies have highlighted gender differences in both visual and motor domains (Chaieb, Antal, & Paulus, 2008; Kuo, Paulus, & Nitsche, 2006). Assuming these gender differences are likely due to hormonal effects, some authors have recently began to only administer tDCS to female participants in the follicular phase of their menstrual cycle (e.g. Pirulli, Fertonani, & Miniussi, 2013). However, this should not be a concern for tDCS studies involving older adult populations, wherein the females are post-menopausal.

4.5 Overall Summary and Objectives

The search for new strategies to maintain the integrity of cognitive functions in older adults is of major importance. Based on the literature reviewed above, tDCS may be an important addition to the repertoire of neuroscientists and clinicians pursuing this challenge. Despite overwhelming evidence supporting tDCS induced modulations in neural activity and behaviour across participants of varying age, a comprehensive explanation of the mechanisms of action of tDCS is still lacking. It is broadly hypothesised that the neuromodulatory effect of tDCS is sub-threshold membrane polarisation, with after effects being mediated by NMDA receptor-dependent changes (Nitsche et al., 2003). The reviewed research also highlights how researchers need to be wary of the multitude of determinants that can influence the magnitude and direction of tDCS induced changes.

Following on from the findings presented in Chapter 2 and Chapter 3, the empirical work within Chapter 5 and Chapter 6 of this thesis will be tailored to assess the viability of tDCS for enhancing error awareness in healthy older adults. One of the most important decisions to be made when designing these studies concerns what region of the cortex to target with tDCS. Although the findings presented in Chapter 3 would suggest that modulation of the pMFC could result in improved error awareness in older adults, the location of the pMFC below the cortical surface renders it, at least directly, inaccessible to tDCS. On the other hand, the dlPFC has been successfully targeted in numerous studies, and not only have strong reciprocal connections between lateral regions of the PFC with pMFC been established (Ridderinkhof et al., 2004), the right dlPFC has been consistently implicated as a region that is critical for accurate awareness of cognitive performance (see *Chapter 1*), which as established in Chapter 2, is closely related to the capacity for error awareness.

Chapter 5 will therefore constitute a series of experiments tailored to assess the effect of tDCS on older adults' performance of the EAT, when anodal versus cathodal tDCS is applied over right versus left dlPFC.

Chapter 6 will extend on Chapter 5 by acquiring EEG data concurrent to tDCS to characterise the electrophysiological correlates of tDCS induced behavioural effects, and also investigate whether effects persist beyond the stimulation period.

Chapter 5: Transcranial Direct Current Stimulation over Right Dorsolateral Prefrontal Cortex Improves Error Awareness Adults

5.1 Introduction

The ability to monitor ongoing performance for occasional errors is essential for adaptive functioning in everyday life. While young healthy adults are typically good at detecting their errors and adjusting their behavior accordingly, this capacity declines with age (Chapter 2; Chapter 3; Rabbitt, 1990), and is also compromised in many clinical conditions (O'Keeffe et al. 2007; Hester et al. 2009; O'Connell et al. 2009; David et al. 2012). The present chapter had the dual goals of establishing whether right dorsolateral prefrontal cortex (dlPFC) plays a causal role in supporting detection of performance errors ('error awareness') and evaluating the potential of transcranial direct current stimulation (tDCS) for remediating awareness deficits in older age.

Although there is a consensus across clinical, brain lesion and neuroimaging studies that the capacity to monitor cognitive performance relies on a broadly distributed network of brain regions that includes prefrontal, parietal temporal and insular cortices (Klein et al. 2007a; Hester et al. 2009), the literature is divided regarding the relative importance of right dlPFC. On the one hand, several studies have demonstrated a strong association between poor awareness of cognitive functioning and hypoperfusion and hypometabolism of right dlPFC in neurodegenerative diseases such as Alzheimer's disease and fronto-temporal dementia (Reed et al. 1993; Starkstein et al. 1995; Antoine et al. 2004; Harwood et al. 2005; Mendez and Shapira 2005). Similarly, awareness of impairment in schizophrenia patients is correlated with right, but not left, dlPFC volume (Shad et al. 2004; Shad et al. 2006). These findings are also consonant with structural and functional data pointing to a specific role of right lateral prefrontal regions in mediating metacognitive abilities in young healthy adults (Fleming et al. 2010; Fleming et al. 2012; De Martino et al. 2013). On the other hand, a role

for right dlPFC was not supported by a number of event-related imaging studies investigating functional activations associated with error awareness (Debener et al., 2005; Hester et al., 2005; Hester et al. 2009; Klein et al., 2007a).

TDCS represents a potentially powerful tool, not only for investigating the contribution of brain regions to specific cognitive functions, but also for developing interventions to ameliorate cognitive deficits (Schulz et al. 2013). Here it was hypothesised that tonically stimulating right dlPFC of healthy older adults with anodal tDCS would lead to a significant improvement in error awareness as measured by the error awareness task (EAT; Hester et al. 2005). This prediction was tested via a sham-controlled cross-over design experiment. Two follow-up experiments were also conducted to explore whether there was evidence of hemispheric and current polarity specific effects. One further replication experiment was additionally carried out to assess the reliability of the findings in the original experiment.

5.2 Methods

Participants

In total 106 healthy older adults aged 65-86 years were recruited for four separate experiments. All participants were right-handed, had no metal implants, had normal or corrected-to-normal vision, and no history of seizures, color blindness or neurological illness. All participants were asked to refrain from consuming caffeine on the day of each testing session. Four participants were excluded because their Mini-Mental State Examination (MMSE, Folstein et al, 1975) score (<24) indicated possible cognitive impairment. Four participants were excluded because their error awareness performance was at ceiling (100%) for the sham condition, and two were excluded for excessively poor error awareness (>2.5 SD below sample mean). One further participant was excluded for failing to abstain from caffeine consumption. As a result, the sample for *experiment 1* consisted of 24 participants (14 female) with a mean age of 72.13 years (SD 6.0, range 65-86); the sample for *experiment 2* consisted of 24 participants (13 female) with a mean age of 69.41 years (SD 4.3, range 65-80); the sample for *experiment 3* consisted of 24 participants (16 female) with a mean age of 69.71 years (SD 4.2, range 65-84); and the sample for *experiment 4* consisted of 24 participants (13 female) with a mean age of 72.08 years (SD 5.7, range 65-83).

Procedures were approved by the ethical review board of the School of Psychology, Trinity College Dublin in accordance with the Declaration of Helsinki. Safety procedures

based on non-invasive brain stimulation approaches were adopted (Poreisz et al. 2007; Rossi et al. 2009) and all participants provided informed consent prior to the beginning of the experiment.

Error Awareness Task

The same version of the EAT that was described in chapter 2 was employed in this study. However, when participants made an error, they were required to signal their awareness of their error with a left button mouse click *as quickly as possible,* as opposed to waiting until the subsequent trial. All participants performed five blocks of the task. The duration of each block was 7.5 min after which the participant rested for 1 minute. Stimulus presentation was controlled by *Presentation* software (Neurobehavioural Systems, USA). It was ensured that all participants were well-practiced and fully understood the requirements of the task before they began their first block of each testing session.

Transcranial direct current stimulation

Stimulation was delivered by a battery-driven DC Brain Stimulator Plus (NeuroConn GmbH, Germany), through a pair of 35 cm^2 saline-soaked sponge electrodes. Current strength was 1mA in all experiments. This produced current densities of 0.028 mA/cm^2 at the skin surface of the scalp.

In all four experiments, participants underwent both real and sham tDCS in a single-blind, crossover manner. The order of the real and sham tDCS conditions were randomized, counterbalanced, and separated by a minimum of 6 days to reduce the risk of carry over effects. For the real stimulation conditions, tDCS was applied for the duration of each of the five blocks of the EAT (5 x 7.5 min) with a ramping period of 20s at the onset and offset. No stimulation was applied during the rest periods between blocks. For the sham conditions, the same electrode montage was used but tDCS was only applied for 20s at the beginning of each block, with a ramping period of 20s at the onset and offset. This procedure ensured that in both real and sham conditions participants experienced the same sensations associated with the onset of tDCS (e.g., tingling sensation; Gandiga et al. 2006).

A summary of the stimulation parameters (guided by Ruff et al., 2013) and participant characteristics for each experiment are presented in **Table 1**. In *experiment 1*, the anode served as the active electrode and was placed over the right dlPFC (F4, according to the 10-20 international system for electroencephalogram electrode placement). In *experiment*

2, the anode was placed over the homologous contralateral area i.e., left dlPFC (F3). In *experiment 3,* the cathode served as the active electrode and was placed over right dlPFC. *Experiment 4* was a replication of *experiment 1* and therefore the anode again served as the active electrode and was placed over the right dlPFC. The reference electrode was placed over the vertex (Cz) in all experiments.

At the end of both Real and Sham stimulation, participants were asked to provide details on the sensations they experienced by completing a questionnaire developed by Fertonani et al. (Fertonani et al. 2010).

Table 5.1 Stimulation parameters and subject characteristics for each experiment

	Stimulation		Electrode location		Participants			
Expt.	**Name**	**Site**	Anode	Cathode	n	Age Mean(SD)	MMSE Mean(SD)	Education Years(SD)
1	Anodal	Right dlPFC	F4	Cz	24	72.13 (6.0)	28.54 (0.8)	14.92 (3.6)
2	Anodal	Left dlPFC	F3	Cz	24	69.41 (4.3)	28.77 (0.8)	13.04 (3.5)
3	Cathodal	Right dlPFC	Cz	F4	24	69.71 (4.2)	28.54 (1.4)	14.58 (3.5)
4	Anodal	Right dlPFC	F4	Cz	24	72.08 (5.7)	28.75 (0.9)	14.17 (3.6)

Statistical Analysis

An aware error was defined as any commission error after which participants pressed the 'awareness' button within 3000 ms. On a small minority of trials participants made a double press of the 'go-trial' (left) button following a No-go trial. Given that it was not possible to determine whether double responses in these instances reflected a failure to click the 'awareness' (right) button in an attempt to signal an error, or an accidental double click of the 'go-trial' button, it was elected to exclude all such double responses from the calculation of error awareness. The Shapiro-Wilk test of normality was used to explore the distribution of each dependent variable. In all four experiments error awareness for Stroop No-go trials was not normally distributed (p <.05) for either real or sham tDCS. To reduce the skewness of error awareness for the stroop targets, and to facilitate the comparison of all variables within the same repeated measures ANOVA, the EA variables for each cell of the multi-factorial ANOVA were subjected to an arcsine transformation. This transformation rendered the distributions normal in experiments 1, 2, and 4, but not *Experiment 3* (p <.05). The potential limitation regarding this violation from normality are highlighted in the discussion. Any other instances where a dependent variable deviated from normality (p <.05) are highlighted, and the appropriate transformation used to render the distribution normal are

described. The effect of tDCS on error awareness and withholding accuracy were assessed using repeated measures analyses of variance (ANOVA). Given that previous studies using the EAT have identified better error awareness for Stroop compared to Repeat No-go trials (O'Connell et al. 2007; Hester *et al.* 2009; O'Connell *et al.* 2009), the effect of tDCS on each of these trial types was analysed separately. Therefore "Intervention" (Real versus Sham tDCS) and "No-go trial type" (Repeat versus Stroop) were included as within-subject factors. Significant interactions were followed up with paired samples t-tests. The effect sizes (Cohen's *d*) of real compared to sham tDCS were also computed. The effect of tDCS on all other EAT variables (i.e., mean Go-trial response time (ms); response time coefficient of variation (ms); mean stimulus duration (ms); mean awareness response time (ms)) was examined using one-way ANOVA. The data from *experiment 1* combined with the data from *experiment 4* (the replication experiment) afforded a sufficiently large sample to investigate whether variables such as Age (Redding and Ziemann, 2010) and Years of Education (Berryhill and Jones, 2012) played a role in responsiveness to the tDCS intervention. Response to the intervention was indexed as the difference score between error awareness for Repeat No-go trials at Real versus Sham stimulation conditions. Bonferroni adjusted correlations (Pearson's *r*) were carried out to examine the respective relationships between response to the intervention and Age, and response to the intervention and Years of Education. It was also of interested to examine whether the effects of the intervention increased or decreased over the duration of the stimulation. To this end, performance on the EAT was split into two halves consisting of the first two blocks and the first half of the 3rd block versus the last two blocks and the latter half of the 3rd block. An ANOVA with "Intervention" (Real versus Sham tDCS) and "Half" (First versus Second half) as within-subject factors was then conducted.

5.3 Results

The means and standard deviations for performance indices on the EAT for real and sham stimulation in each of the experiments are provided in **Table 5.2**.

Experiment 5.1: Anodal Stimulation over Right dlPFC

There was no main effect of intervention on error awareness (p = .068), but a significant Intervention x No-go trial type interaction ($F(1,23)$ = 4.42, p = .043) was observed. Paired sample t-tests indicated that the interaction was driven by a tDCS-induced improvement in error awareness for Repeat No-go trials ($t(23)$ = 2.51, p = .02, d = .51) that

was absent for Stroop No-go trials (p = .709, d = -.08; see Figure 1). There was no main effect of tDCS on withholding accuracy (p = .6) and there was no Intervention x No-go trial type interaction (p = .6), indicating that the adaptive adjustment of task difficulty was successful. There was also no effect of tDCS on mean Go-trial response time, response time coefficient of variation, or mean stimulus duration (all p > .05). Therefore, anodal tDCS applied to the right dlPFC was associated with a specific improvement in error awareness for Repeat No-go trials.

Main effects of No-go trial type were observed for both error awareness (F(1,23) = 178.33, p < .001) and withholding accuracy (F(1,23) = 7.70, p = .05). The former indicated significantly greater error awareness for Stroop compared to Repeat No-go trials across both Real and Sham sessions, while the latter indicated significantly greater withholding accuracy for Repeat compared Stroop No-go trials across both Real and Sham sessions. Both these main effects were recapitulated in the three subsequent experiments.

Experiment 5.2: Anodal Stimulation over Left dlPFC

There was no main effect of intervention on error awareness (p = .35, d = -.04) and no Intervention x No-go trial type interaction (p = .9). In this experiment, withholding accuracy was not normally distributed for either real or sham tDCS. This variable was therefore subjected to an arcsine transformation to improve the skew of the distribution. There were no significant effects of intervention on withholding accuracy, or on any other task variables (all p > .05).

Experiment 5.3: Cathodal Stimulation over right dlPFC

There was no main effect of intervention on error awareness (p = .96, d = .09), no Intervention x No-go trial type interaction (p = .216) and no significant effects on any other task variables (all p > .05).

To investigate whether *experiment 1* yielded a reliable difference relative to experiments 2 and 3, a two way repeated measures ANOVA was conducted with Intervention and No-go trial type as within-subject factors and Experiment (1 vs 2 vs 3) as a between subject. This revealed a significant No-go trial type by Intervention by Experiment interaction (p = .001), reflecting that a tDCS related change in performance was only evident for Repeat No-go trials in *experiment 1*."

Experiment 5.4: Anodal Stimulation over right dlPFC (Replication Study)

The pattern of results in *experiment 4* were very similar to those observed in *experiment 1* (**Figure 5.1**). tDCS was not associated with a main effect of Intervention (p = .115), but an Intervention x No-go trial type interaction ($F(1,23) = 3.43$, p = .084, two-tailed) reached trend-levels of significance when two-tailed thresholds were applied, and reaching significance when one-tailed thresholds were applied. The paired sample t-tests indicated that tDCS produced a significant improvement in error awareness for Repeat No-go trials ($t(23) = 2.05$, p = .052, d = .42) that was absent for Stroop No-go trials (p = .5, d = -.13). There was no effect of tDCS on any other task variables (all $p > .05$). Therefore, anodal tDCS applied over the right dlPFC was once again associated with a specific improvement in error awareness for Repeat No-go trials.

Table 5.2 Performance indices on the error awareness task for real and sham stimulation for each experiment: mean (SD)

	Real Stimulation	Sham Stimulation
Experiment 1		
Repeat Accuracy (%)	75.96 *(12.18)*	75.56 *(15.47)*
Stroop Accuracy (%)	68.12 *(13.80)*	66.55 *(16.13)*
Repeat Awareness (%)*	56.92 *(22.72)*	44.55 *(20.38)*
Stroop Awareness (%)	88.08 *(13.53)*	89.14 *(11.39)*
Experiment 2		
Repeat Accuracy (%)	73.09 *(18.37)*	75.29 *(20.47)*
Stroop Accuracy (%)	60.69 *(20.91)*	62.17 *(20.88)*
Repeat Awareness (%)	55.74 *(28.25)*	53.75 *(23.9)*
Stroop Awareness (%)	87.56 *(17.91)*	87.06 *(14.67)*
Experiment 3		
Repeat Accuracy (%)	73.45 *(15.32)*	72.23 *(14.37)*
Stroop Accuracy (%)	60.57 *(16.57)*	61.49 *(16.99)*
Repeat Awareness (%)	64.81 *(16.94)*	68.07 *(21.96)*
Stroop Awareness (%)	93.97 *(7.41)*	92.03 *(9.13)*
Experiment 4		
Repeat Accuracy (%)	74.65 *(15.39)*	78.23 *(11.79)*
Stroop Accuracy (%)	64.52 *(17.08)*	65.95 *(14.35)*
Repeat Awareness (%)*	65.93 *(24.03)*	56.19 *(24.16)*
Stroop Awareness (%)	93.54 *(11.50)*	95.20 *(8.07)*

* $p<.05$

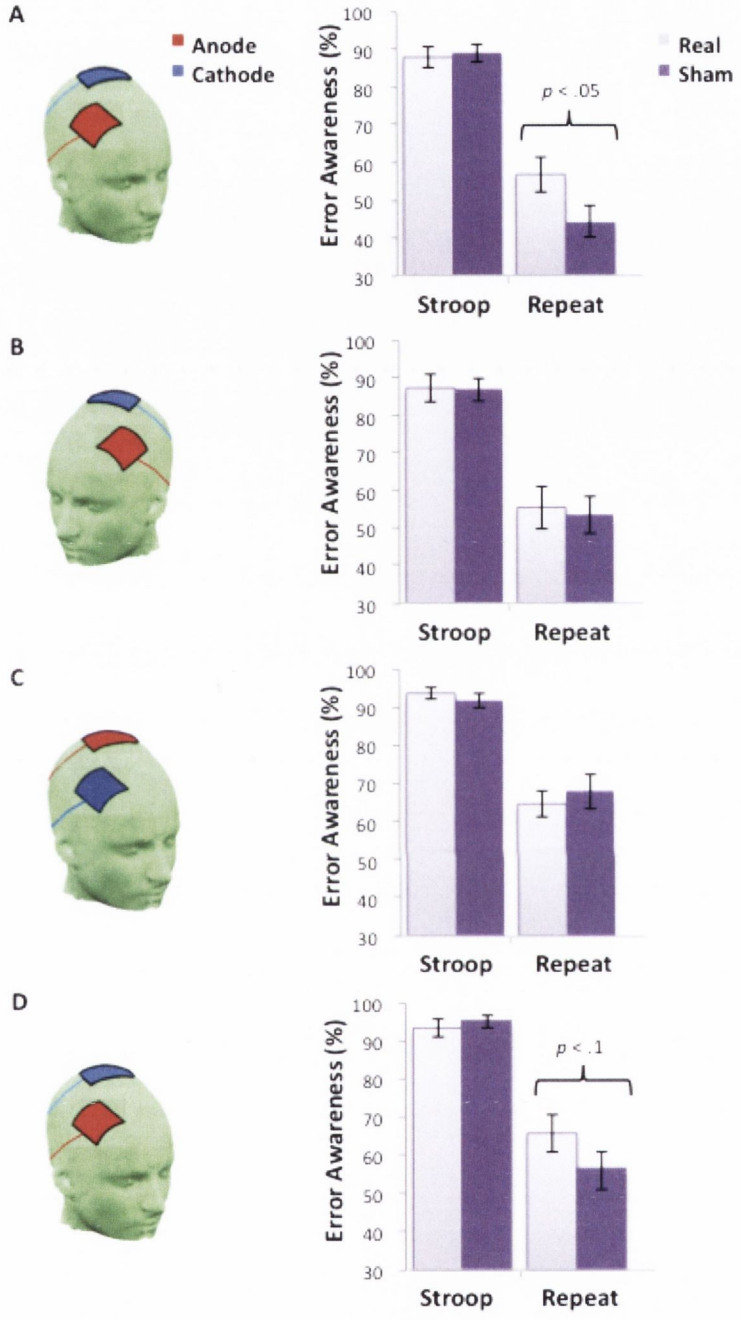

Figure 5.1 Effect of transcranial direct current stimulation (tDCS) on error awareness in experiments 1, 2, 3 and 4. (A) Experiment 1: anodal tDCS over right dorsolateral prefrontal cortex (dlPFC) was associated with a significant improvement in error awareness for Repeat No-go trials. **(B)** Experiment 2: anodal tDCS over left dlPFC was not associated with any changes in error awareness. **(C)** Experiment 3: cathodal tDCS over right DLPFC was not associated with any changes in error awareness. (**D**) Experiment 4: The results of experiment 1 were recapitulated in experiment 4: anodal transcranial direct current stimulation over right dorsolateral prefrontal cortex was again associated with a significant improvement in error awareness for Repeat No-go trials.

When the data for experiments 1 and 4 were combined error awareness was normally distributed for both Repeat and Stroop No-go trials for both real and sham tDCS. A repeated measures ANOVA on the combined revealed a significant main effect of Intervention ($F(1,47) = 9.21$, $p = .004$, $d = .41$), and a significant Intervention x No-go trial type interaction ($F(1,47) = 7.55$, $p = .008$) were observed, with follow up-tests indicating significant improvement in error awareness for Repeat No-go trials ($t(47) = 3.24$, $p = .002$, $d = .47$) but no significant changes for Stroop No-go trials ($p = .5$, $d = -.10$). Again, there was no effect of tDCS on any other task variables (all $p > .05$).

While there was a substantial improvement in error awareness for Repeat No-go trials at the group level, it was found that there were a number of participants for whom there was either no change, or a deterioration, with anodal tDCS (see **Figure 5.2**).

Moderating Factors

Considering there was substantial variability in response to the intervention, we sought to examine whether factors such as Age or Years of Education had a moderating role in the observed effects. Given the ceiling effects for Stroop No-go trials, response to the intervention was considered in terms of changes in error awareness for Repeat No-go trials only. There was no association between response to the intervention and Age ($p = .7$), but there was a non-significant trend toward a positive correlation between response to the intervention and Years of Education ($r = .278$, $p= 0.055$). It was also of interest to examining whether the effects of the intervention varied as function of stimulation duration. The analysis of time on task effects revealed a main effect for Intervention ($p = .008$) and a main effect for Half ($p = .001$) such that error awareness for Repeat No-go trials decreased with time-on-task. There was no Intervention x Half interaction ($p = .2$).

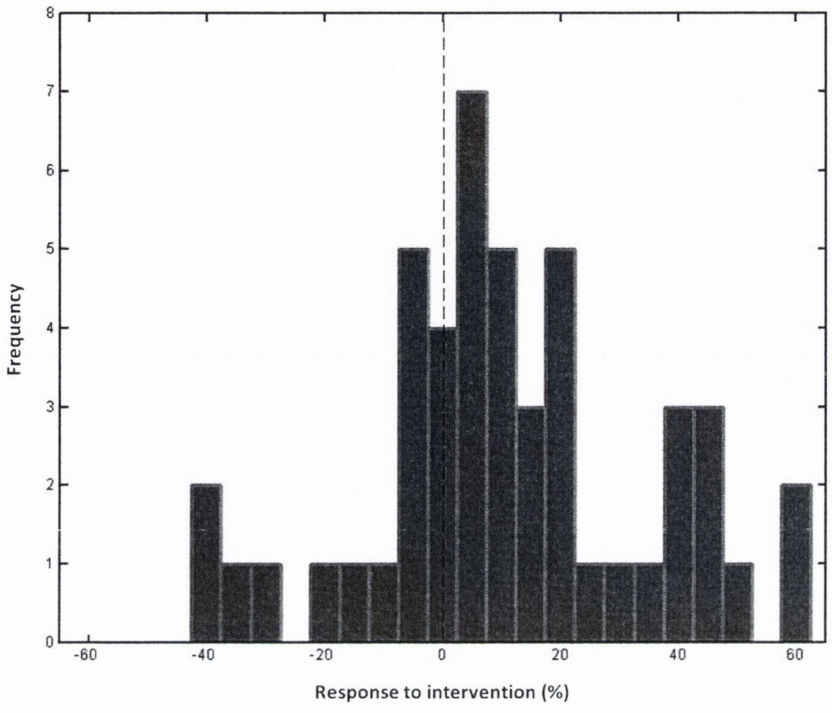

Figure 5.2 Inter-individual variability in response to intervention. Histogram displaying inter-individual variability in response to the intervention. Response to the intervention was defined as each subject's mean difference score between percentage error awareness for Repeat No-go trials at real versus sham stimulation conditions. Positive values indicate better error awareness for Repeat No-go trials at Real compared to Sham stimulation.

Sensations Questionnaire

The results of the sensations questionnaire indicated that all participants tolerated the stimulation without discomfort. Although no strong sensations were reported, Real compared to Sham anodal stimulation, was associated with greater levels of "itchiness" for the three anodal stimulation studies (all $p < .05$). No other sensation was perceived to differ across the Real and Sham conditions (all $p > .05$). To determine whether the perceived itchiness was associated with the performance-facilitating effect of tDCS, the correspondence between the intensity of the perceived itchiness and levels of error awareness at real stimulation was examined. This analysis revealed no significant association between perceived itchiness and overall error awareness or repeat error awareness for any of the experiments (all $p > .05$). The results of the sensations questionnaire therefore indicate that perceived sensation did not influence performance.

5.4 Discussion

The aim of the present chapter was to assess whether the application of tDCS over right dlPFC could modulate older adults' awareness of their performance errors. In two separate experiments a reliable increase in the number of errors that were signaled by older adults during anodal stimulation to right dlPFC, relative to sham stimulation was demonstrated. Increases of 12% and 10% in error awareness for Repeat No-go trials were observed in experiments 1 and 4, respectively. The improvement in error awareness could not be accounted for by changes in accuracy or slowed response times, as both of these task variables remained unchanged across Real and Sham stimulation conditions. It was additionally demonstrated that while anodal tDCS stimulation was effective when applied to right DLFPC, no change in performance was observed when left dlPFC was targeted. This study therefore provides novel evidence that dlPFC regions subserving error awareness are predominantly lateralized to the right hemisphere.

The EAT involves two distinct No-go trial types, a design feature that is included to increase the overall error rate and hence to increase the probability that some errors will go unnoticed (Hester et al., 2005). TDCS-related improvements in error awareness were only evident for Repeat No-go trials. This observation merits consideration of whether tDCS affected a cognitive process that is specific to Repeat No-go trials. For instance, it may be argued that Repeat No-go rely more on memory than Stroop No-go, and the observed tDCS related improvements may therefore be due to improved memory capacity. However, this does not reconcile with the fact that awareness and error rates are uncorrelated (O'Connell et al, 2009), that task difficulty and performance accuracy did not vary across Real and Sham conditions, and the observation that awareness on the EAT correlates with awareness of cognitive function in everyday life (Chapter 1). A more plausible explanation for the absence of an effect on Stroop No-go may be that performance was close to ceiling (average of 91% across all experiments), likely leaving little room for any further improvements. Previous work suggests that tDCS-induced improvements may not be observed when baseline levels of performance are already high (Kang et al. 2009; Tseng, Hsu, Chang et al., 2012), and that facilitatory effects are more pronounced when there are greater levels of impairment (Hummel et al. 2006).

Cathodal stimulation over right dlPFC did not induce any behavioral changes, relative to sham stimulation. This finding is consistent with several other studies that have failed to modulate cognitive functions using cathodal tDCS (Fregni et al. 2005; Cerruti and Schlaug 2009; Fertonani et al. 2010; Friederici et al. 2013). A number of possible explanations have been proposed to explain the apparent resilience of cognitive functions to cathodal

stimulation (for a review on theses aspects see Miniussi et al. 2013). For instance, the significant cytoarchitectonic differences between neurons in the motor and frontal cortices are likely to play a role in the differential sensitivity of motor and cognitive functions to changes based on the direction of the current flow. The impact of tDCS may also depend on the initial state of neuronal activation. While anodal stimulation might precipitate cognitive enhancement by boosting the excitability of neurons that by default are not reaching the threshold to contribute to the cognitive function, cathodal stimulation might not be sufficient to significantly impede the firing of neurons that are already activated by engaging in the cognitive task (Miniussi et al. 2013). The absence of cathodal stimulation effects on behavior might also reflect the compensatory recruitment of other regions within the cognitive networks (Jacobson et al. 2012). However, due consideration should also be given to the fact that the type II error likelihood may have been inflated due to the error awareness data for Stroop No-go trials persisting to violate the assumption of normality following the arcsine transformation.

Because tDCS is associated with sensations at the electrode site (Gandiga et al. 2006), there is a potential concern that greater somatic stimulation might induce expectancy effects. To investigate the relationship between expectancy and behavior, the correspondence between perceived sensations induced by tDCS and error awareness at Real and Sham conditions was examined. Although no strong sensations were reported, real tDCS did induce more itchiness compared to Sham tDCS across experiments 1, 2 and 4. However, there was no association between the intensity of participants' perceived itchiness and levels of error awareness for Real tDCS, for any of the experiments. Furthermore, if perceived itchiness was the basis for the improvement in error awareness for experiments 1 and 4, the perceived itchiness in experiment 2, should have been associated with comparable improvements in error awareness. These findings indicate that the facilitatory effects of tDCS were not linked to perceived sensations or expectancy.

The finding that anodal tDCS produced an effect when applied over right, but not left, dlPFC provides new evidence for a dominant role of right dlPFC in mediating awareness. While this finding is highly consistent with the clinical and brain lesion literature (Antoine et al. 2004; Harwood et al. 2005; Hoerold et al., 2013; Mendez and Shapira 2005; Reed et al. 1993; Shad et al. 2004; Shad et al. 2006; Starkstein et al. 1995), it does not reconcile directly with event-related functional imaging work in which right dlPFC is often not implicated in error awareness (Debener et al., 2005; Hester et al., 2005 Hester et al. 2009; Klein et al., 2007a). However, event-related functional imaging research to date has focused on error-evoked activations. While this approach serves to isolate structures that are activated during

the processing of an erroneous action, awareness may be largely determined by adaptive neural activity prior to target onset. For example, previous research has demonstrated a close relationship between the ability to maintain a vigilant state and error awareness (Chapter 2; Hoerold et al., 2008; O'Keefe et al., 2007; McAvinue et al. 2005, Shalgi et al 2007; Robertson, 2010). Nonetheless, it is clear that several other regions are implicated in error awareness, so it remains to be seen whether right dlPFC is the only stimulation site through which such tDCS induced gains can be achieved.

It is also important to consider the potential influence of changes in neural excitability under the reference electrode (e.g. Nitsche et al., 2007). Considering no effects of stimulation were observed in *experiment 2*, where the reference electrode was also placed over Cz, the observed effects are unlikely to be due to neuromodulatory changes in the vicinity of the reference electrode. In addition, the scalp location Cz corresponds to the confluence of the right and left central sulcus, which has not been implicated in any study of error awareness to date. That said, it is not known how deep, lateral, or anterior the right lateralized stimulation effects were. Although no modeling study to date has simulated the electrode montage employed in the present study, studies have shown that similar montages result in diffuse current flow through the brain (Sadleir et al., 2010), particularly in brain regions that are functionally related to the stimulated area (Keeser et al., 2011; Meinzer et al., 2013). Therefore, the possibility that the performance facilitating effect of tDCS was mediated through the stimulation of other brain regions that have been shown to be important for error awareness, such as pMFC (Chapter 3; Murphy et al., under review; Orr & Hester, 2012) cannot be excluded. It will be of value for future research to combine tDCS, neuroimaging and modeling to help clarify how tDCS is influencing the underlying cortex and modulating error awareness.

It will also be important for future studies to examine the extent to which these findings generalize to populations other than older adults. While there is compelling evidence of a strong association between the capacity for awareness and right dlPFC across several different populations, research also suggests that the natural ageing process is associated with a general increase in frontal lobe recruitment (e.g., Davis et al. 2008). Considering this, it is important to acknowledge the possibility that the observed facilitatory effects of tDCS on error awareness may to some degree be attributable to functional reorganisation in the ageing brain.

While the present study has demonstrated that a single session of anodal tDCS can result in immediate improvements in error awareness, the maintenance of the effect beyond the period of stimulation was not assessed. Further work will therefore be required to

determine the viability of tDCS as a tool for the long-term remediation of awareness deficits. Encouragingly, previous studies have shown that multiple consecutive sessions of anodal tDCS can induced gains in cognitive functioning can persist for several weeks (Boggio et al. 2012; Doruk, Gray, Bravo, Pascual-Leone, & Fregni, 2014; Joen & Han, 2012) The translational potential of these findings is also presently limited by the substantial inter-individual variability in response to the tDCS. Previous work has already highlighted several factors that may contribute to this kind of variability, including differences in neurotransmitter efficiencies (Brunoni et al., 2013; Ridding & Ziemann, 2010), genetic polymorphisms (Ridding & Ziemann, 2010), participant specific anatomy (Datta et al., 2012), age (Ridding and Ziemann, 2010), and years of education (Berryhill and Jones, 2012). Improving the understanding of these, and other determinants, will be critical for the application of these findings to clinical rehabilitation.

The findings of the present chapter have both theoretical and practical implications. From a theoretical perspective, the findings support the view that right lateralised dlPFC structures play a critical role in mediating awareness of cognitive performance. At the translational level, the observed facilitatory effect of tDCS may be fruitful as a preliminary step towards optimising tDCS as a tool to enhance error awareness in older adults, as well as other clinical populations afflicted by error awareness deficits. Importantly, it has previously established that error awareness on the EAT is representative of awareness on real-word tasks (Chapter 2). Prioritising the remediation of error awareness deficits may indeed confer benefits to other cognitive functions by providing impetus to implement compensatory strategies, or fostering willingness to engage in, and adhere to, therapeutic interventions.

Chapter 6: The Electrophysiological Basis of tDCS-Induced Improvements in Error Awareness

6.1 Introduction

In Chapter 3 it was found that older adults' error awareness deficits are associated with age-related declines in the encoding of error evidence, as indexed by MF theta, and in the subsequent accumulation of that evidence during second-order decision making, indexed by the Pe. In Chapter 5 it was demonstrated that the application of anodal tDCS over right dlFPC of older adults was reliably associated with an improvement in error awareness. The primary objective of the present chapter is to determine whether tDCS induced improvements in error awareness, are mediated by changes in the electrophysiological indices of evidence encoding and accumulation.

It is now widely accepted that complex brain functions, such as co-ordinated movement and language, as well as performance monitoring and error awareness, depend critically on dynamic interactions between brain regions (cf. Cocchi, Zalesky, Fornito, & Mattingly, 2013). This has led to the notion of *functional connectivity networks,* wherein distributed neural regions transiently interact to execute a particular function (Cocchi et al., 2013). Aberrant interactions between nodes of networks play a critical role in common and debilitating psychiatric and neurological conditions ranging from depression to epilepsy (Menon, 2011), and disruption of functional connectivity between network nodes has also been identified as a hallmark of cognitive ageing (Goh, 2011; Hedden, Van Dijk, Becker et al., 2009).

Consistent with the concept of such distributed neural networks it is becoming increasingly apparent that the application of tDCS over a discrete area of the cortex is associated with distributed neural network effects that are contingent on the anatomical and

functional connectivity between the directly targeted cortical regions and the rest of the brain (Keeser et al., 2011; Lang et al., 2005, Meinzer et al., 2013; Najib & Pascual-Leone, 2011; Russell et al., 2013; Sadleir et al., 2010). For instance, using spectral power analysis and low resolution electromagnetic tomography (LORETA), Keeser et al. (2011) were able to deduce that anodal tDCS applied over left dlPFC modulated activity in a network involving the medial frontal gyrus, the pMFC and the subgenual cortex, and they furthermore found that this effect on neural activity was associated with a lower error rate, faster RTs, and increased amplitudes of the P2 and P3 ERP components during a working memory task. Also using LORETA, Conti and Nakamura (2014) found that bilateral tDCS over dlPFC modulated drug-cued reactivity in the pMFC of crack-cocaine addicts. Therefore, although the neuromodulatory effects of tDCS are typically most pronounced in the local region of the cortex underlying the tDCS electrodes (Wagner et al., 2014), distant cortical and subcortical structures are also often modulated to some extent via trans-synaptic effects (Hummel & Cohen, 2006; Najib & Pascual-Leone, 2011).

Najib and Pascual-Leone (2011) highlight how the impact that tDCS may have on distributed nodes of a network depends not only upon the type of local modulation of excitability induced in the directly targeted region, but also upon whether the connections between the targeted brain region and distant nodes of the network are excitatory or inhibitory. For instance, increasing the activity in a discrete cortical region that sends inhibitory projections to a particular distant node, will suppress activity in that distant node. Conversely, increasing the activity in the same cortical region will enhance activity in a region that receives excitatory connections from the targeted brain area.

The implication of the right dlPFC in error awareness likely reflects its general role in exerting top-down control in situations that require the maintenance and manipulation of task relevant information, or vigilance (Chapter 1; Chapter 5). However, it seems plausible that gains in error awareness via the application of anodal tDCS over right dlPFC may be achieved through secondary modulation of a number of other functionally related regions, such as the pMFC.

While there has been a long-standing consensus that the pMFC is a primary neural substrate of the performance monitoring system (Ridderinkhof et al., 2004), its role in conscious detection of errors has been a matter of considerable debate, with several early neuroimaging studies of error awareness suggesting that error-evoked pMFC activity was not sensitive to error awareness (Endrass et al., 2005; Hester et al., 2005; Klein et al., 2007; Nieuwenhuis et al., 2001). However, more recently, growing evidence from both EEG and fMRI modalities has supported an important role for the pMFC in the emergence of error

awareness (Hester et al., 2012; Maier et al., 2008; Murphy et al., under review; Orr & Hester, 2012; Steinhauser & Yeung, 2010; Wessel et al., 2011). As discussed in previous chapters, the notion that MF theta oscillations encode the response conflict that arises from the competition between two or more conflicting choices (Cohen, 2014; Cohen & Cavanagh, 2011), is also consistent with the notion that the pMFC plays an important role in error awareness (see Chapter 1; Chapter 3). Further, the finding that MF theta distinguishes between aware and unaware errors from an early latency relative to error commission in young adults (Murphy et al., under review) has now been found to generalise to an older adult sample (Chapter 3).

As mentioned in Chapter 1, functional interactions between the pMFC and the dlPFC are invariably observed during the regulation of goal-directed behaviour (Cavanagh et al., 2009; Fassbender et al., 2004; Hester, Fassbender & Garavan, 2004, Kerns, 2006; Kerns et al., 2004; Ridderinkhof et al., 2004). Indeed an influential model of cognitive control proposes that the pMFC and dlPFC have interactive roles in detecting instances that require more cognitive control, and the implementation of the requisite cognitive control, respectively (Botvinick, et al., 2001; Braver & Cohen, 2000; Carter & van Veen, 2007; Miller & Cohen, 2001; Norman & Shallice, 1986; Ridderinkhof, et al., 2004; Sohn, Albert, Jung, Carter, & Anderson, 2007). In accord with this, the degree of BOLD activity on high-conflict and error trials robustly predicts activity in the lPFC on the subsequent trial (Kerns, 2006; Kerns et al., 2004). Cavanagh et al. (2009) have also shown that error-related theta phase synchronisation between pMFC and lPFC electrode sites predicts post-error slowing on a trial-to-trial basis. The lack of similar functional connectivity between the pMFC and comparably distant posterior sites corroborates the argument for a specific functional linking between pMFC and lPFC, and not mere volume conduction (Cavanagh et al., 2009). A more tonic coupling has additionally been found between BOLD activity in both structures, which is believed to reflect the maintenance of a strong tonic task set (Fassbender et al., 2004, Hester et al., 2004).

Studies have also found that patients with focal lesions of the lPFC demonstrate abnormal pMFC activity in response to errors (Gehring & Knight, 2000; Ullsperger, von Cramon, & Müller, 2002). Importantly, such studies provide evidence against the possibility of a unidirectional flow of information between the pMFC and lPFC. They instead suggest that performance monitoring and the regulation of cognitive control may be achieved through intricate reciprocal projections between these two structures (Ridderinkhof et al., 2004; Ullsperger, 2006), and accordingly provide a strong basis for hypothesising that the

pMFC may be involved in mediating the tDCS-induced improvements in error awareness that were observed in Chapter 5.

The combined use of tDCS and EEG represents a valuable method for probing the mode of action of tDCS and its influence on distributed nodes of networks. Owing to the technical problems that can be encountered during EEG-tDCS co-registration, the majority of studies that have used the combined methodologies, to date, have adopted the so-called 'Offline' approach of evaluating the short- and long-term electrophysiological after-effects induced by tDCS. However, due to an increased understanding of how the technical challenges of acquiring EEG concurrent to tDCS can be overcome (see Chapter 4) a growing number of studies are employing the 'Online' approach and successfully acquiring real-time information on the electrophysiological effects that are directly associated with tDCS (Accornero et al., 2007; Accornero, Cappozza, Pieroni et al., 2014; Faria et al., 2012; Romero Lauro et al., 2014; Mangia et al., 2014; Schestatsky et al., 2013; Soekadar et al., 2014; Strigaro et al., 2014; Wirth et al., 2011).

In the present chapter, both the Online and Offline electrophysiological and behavioural effects of anodal tDCS over right dlPFC are evaluated in a sample of healthy older adults. In so doing, this chapter aims to extend on Chapter 5 in two main ways: 1) to elucidate the mode of action of tDCS and its influence on regions beyond the directly targeted dlPFC; and 2) to establish whether the gains in error awareness persist beyond the stimulation period. Given that the electrophysiological correlates of better error awareness include greater response-locked MF theta power, and a steeper as well as earlier peak, of the Pe (Chapter 3), it is hypothesised that tDCS induced gains in error awareness will be associated with greater response-locked MF theta power, as well as a steeper rate of rise, and earlier peak, of the Pe.

6.2 Methods

Participants

Thirty-one healthy older adults participated in the study. Three participants were excluded due to poor accuracy on the task (<30% correctly withheld No-go trials). The remaining sample consisted of 15 males and 13 females with a mean age of 73.4 (*SD* 5.1, range 65-85). 'Offline' blocks were not obtained for one participant from this sample and therefore Offline analyses were based on a sample that consisted of 14 males and 13 females

with a mean age of 73.6 (*SD* 5.1, range 65-85). Exclusion criteria were left-handedness, visual impairment, history of neurological or psychiatric illness, neurological insult, drug or alcohol abuse, and/or reporting current use of anti-psychotic or anti-depressant medications. All participants were asked to refrain from consuming caffeine on the days of each testing. Procedures were approved by the Trinity College Dublin ethical review board in accordance with the Declaration of Helsinki, and all participants provided written informed consent.

The Error Awareness Task

All participants performed five 'Online' blocks and three 'Offline' blocks of the EAT. The same version of the EAT that was used in the experiments in Chapter 2 and Chapter 5 was employed again but an additional five No-go trials (3 Repeat, 2 Stroop) were added to each block to increase the number of potential error trials available for analysis. It was ensured that all subjects were well practiced and fully understood the requirements of the task before they began their first block of each testing session.

Transcranial Direct Current Stimulation

The same stimulation parameters and electrode montage used in experiments 1 and 4 of Chapter 5 were implemented again. However, instead of saline solution, high chloride electrode paste (ABRALYT HiCl) was used to mimimise the electrode-scalp impedance. This was chosen for two reasons. Firstly, during pilot testing it was observed that the electrode paste gave rise to more stable levels of impedance throughout the testing session compared to the saline solution. This was particularly important for the simultaneous tDCS-EEG set-up as even small fluctuations in impedance can interfere with the EEG. Secondly, the adhesive properties of the paste helped to ensure that the placement of the EEG cap did not cause the tDCS electrodes to shift on the scalp. In order to avoid tDCS artifacts in the EEG, caution was taken to ensure the tDCS electrodes and conductive paste were never in contact with the EEG electrodes and leads.

As in the previous tDCS experiments (Chapter 5), participants underwent both Real and Sham tDCS in a single-blind, crossover manner. The order of the Real and Sham conditions was randomised, counterbalanced, and separated by a minimum of 6 days. For the Real condition, tDCS was applied for the duration of each of the five 'Online' blocks of the EAT (5 x 7.7 min) with a ramping period of 20s at the onset and offset. For the Sham condition, the same electrode montage was used but tDCS was only applied for 20s at the beginning of each block, with a ramping period of 20s at the onset and offset. During pilot

testing it was noted that the ramping periods of the stimulation produced artifacts in the EEG recording (cf. Miniussi et al., 2012; Schestatsky et al., 2014). Accordingly, for the Real condition, the stimulator was turned on and the current was allowed to ramp and settle for 30 s before any data were recorded. Similarly, the ramping down did not begin before the end of each block. For the Sham condition, the stimulator was turned on for a full minute before data recording began. This minute comprised the 20 s stimulation at 1 mA and a ramping period of 20 s at the onset and offset. Following the 5th block of the EAT the Stimulator was turned off and participants had a one minute break before proceeding to complete the three 'Offline' blocks.

Electroencephalography Acquisition and Pre-processing

Continuous EEG data were acquired using an ActiveTwo System (BioSemi) from a cap with 64 electrode sites placed in accordance with the standard 10/20 set-up. The BioSemi system lends itself well to recording during tDCS stimulation because of its large amplitude range, which avoids electrode saturation. Due to the positioning of the tDCS electrodes (see **Figure 6.1**), EEG data could not be recorded from the following 11 electrode sites: AF4, F2, F4, F6, FC4, C1, Cz, C2, CP1, CPz and CP2. Horizontal and vertical eye movements were recorded using two horizontal EOG electrodes placed at the outer canthus of each eye and two vertical electro-occulogram (EOG) electrodes positioned above and below the left eye, respectively. EEG data were processed using custom scripts in MATLAB drawing on EEGLAB formulae for reading data files and spherical spline interpolation of noisy channels (Delorme & Makeig, 2004). The EEG data were re-referenced offline to an average reference that excluded electrodes that did not have an electrode in the homologous location on the right hemisphere of the scalp (i.e. AF3, F1, F3, F5 and FC3). Epochs of 7.7 seconds were extracted around each no-go target trial (-4.2 to 3.5 s) for each block. The epochs from all Online blocks and all Offline blocks were then concatenated separately for each participant. In a preliminary artifact rejection stage, trials were rejected if any scalp channel exceeded an absolute value of 250μV at any time during the epoch. Independent components analysis (ICA) was subsequently conducted on the remaining epochs to remove blinks, eye movements, and 'popping' electrodes, based on visual scrutiny of component topographies and time courses (Debener et al., 2007, 2008). A high pass filter cut-off of 0.5 Hz was applied to the data to facilitate the implementation of the ICA, but the acquired weights were subsequently back-projected on to the raw data, upon which only a low-pass filter of 40 Hz was applied. A final rejection criterion was applied whereby any trials for

which one or more of the channels used to measure the Pe, ERN, medial-frontal theta or occipital alpha exceeded an absolute value of 100μV were eliminated.

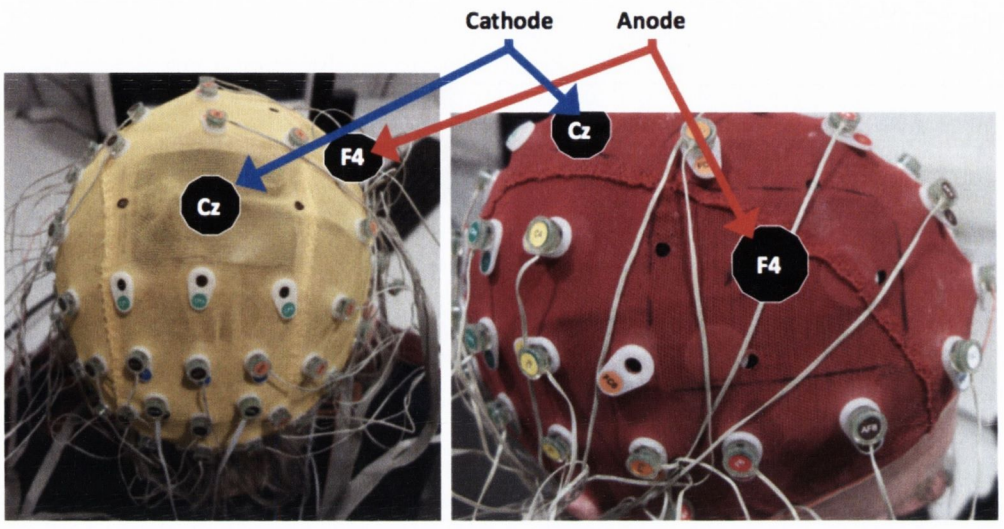

Figure 6.1 Set-up for co-registration of transcranial direct current stimulation and electroencephalography. Positioning of the Cathode and Anode at electrode sites Cz and F4, respectively

Event-Related Potentials Analyses

Grand-average peak latency and amplitude of the ERN were derived from the average signal across electrodes FCz FC1 and FC2, and were defined as the timing and amplitude, respectively, of the minimum voltage in the 100 ms following the error. To reduce the number of comparisons only the grand-average Pe waveform aligned to the erroneous response was extracted in this study. By comparing the amplitude of the grand-average signal across the available centro-parietal electrodes it was apparent that the Pe component was maximal over electrodes P1 and Pz. Accordingly, the grand-average measures of peak amplitude, peak latency and build-up rate of the component were derived from the average of the signal across these electrodes. Amplitude was defined as the mean amplitude within 400 ms to 600 ms post-error, peak latency was defined as the maximum amplitude occurring in a window from 150 ms to 800 ms post-error, and the build-up rate was defined as the slope of a straight line fitted to the waveform of each subject using a window from 150 ms to 300 ms post-error.

Single-trial measures of Pe peak latency, amplitude, and build-up rate were extracted and averaged for each participant to further characterise the dynamics of the Pe and their relationship with Error Awareness and Mean Awareness RT at both Real and Sham tDCS. As in Chapter 3, 6 Hz low-pass filter was applied to mitigate the noise inherent in these single-trial measures (Spencer, 2005). Again as in Chapter 3, single-trial peak latency and amplitude were defined as the timing and amplitude, respectively, of the maximum voltage from 200 ms post-error press to the slowest awareness press for each participant at each tDCS condition. Build-up rate was defined as the slope of a straight lined fitted to each single-trial Pe in the 100 ms window preceding the peak latency of each trial.

Time-Frequency Analyses

Time-frequency analysis was carried out using the same procedure as implemented in Chapter 3 aside from the following deviations. First, it was apparent from the event-related spectral perturbation (**Figure 6.5**) that although the characteristic burst in theta power exhibited the same temporal distribution (-200 to 500 ms), it fell within a slightly narrower frequency range of 2-6 Hz compared to that observed in Chapter 3. Second, visual inspection of the spatial topography indicated that an average of the signal across electrodes FC1, FC2 and FCz would best capture the signal. Accordingly, theta power was defined as the mean power of the average signal over electrodes FC1, FC2 and FCz, within the 2-6 Hz frequency range, from -200 to 500 ms relative to the response. Third, in the present study, in order to test the frequency band-specificity of any theta effects, response-locked occipital alpha was also analysed. Occipital alpha power was defined as the mean power of the average signal over electrodes O1, O2 and Oz, within the 8-14 Hz frequency range, from -200 to 500 ms relative to the response. The final deviation from Chapter 3 was that due to an insufficient number of unaware error trials in this study, time-frequency analysis could only be performed on Standard Go-trials and Aware error trials. As in Chapter 3, single-trial MF theta power was defined as the mean power from -100 to 400 ms relative to error commission.

Statistical Analysis

For all behavioural and EEG variables, values which deviated more than 3 standard deviations from the mean were identified and excluded from all subsequent analyses. For one set of analyses, namely, the behavioural analysis of the error awareness data for the EEG subgroup, it was found that the variables error awareness scores for Stroop No-go trials only

met the assumption for normality when one participant was removed whose score deviated 2 standard deviations from the mean.

As in Chapter 3, trials where the awareness press occurred after the onset of the next stimulus were counted as an aware error when calculating participants' average behavioural measures of error awareness, but were omitted from all ERP analyses. Also, similar to Chapter 3, only participants who provided least 12 aware errors, following artifact rejection, at both Real *and* Sham tDCS conditions were included in the EEG analyses (Larson et al., 2010; Olvet & Hajcak, 2009). This led to a reduced sample of 18 participants for the Online analyses, and 16 participants for the Offline analyses. Repeated measures ANOVA with "Intervention" (Real versus Sham) and "No-go trial type" (Repeat vs Stroop) as within-subject factors, were used to assess the effect of tDCS on error awareness, withholding accuracy, mean awareness RT and mean awareness RT coefficient of variation (CV). The latter is a stringent measure of intra-individual performance variability (Bellgrove, Hester, & Garavan, 2004; Murphy et al., 2012; Stuss, Murphy, Binns, & Alexander, 2003), calculated by dividing the standard deviation (SD) in RT by the mean. Significant interactions were followed up with paired samples t-tests. The effect sizes (Cohen's d) of Real compared with Sham were also computed. Although it was apparent from Chapter 5 that the tDCS effects were specific to error awareness for Repeat No-go trials, Murphy et al. (under review) have demonstrated that there is no effect of No-go trial type on the dynamics of the Pe. Therefore, in order to maximize the number of trials available for analysis Repeat and Stroop No-go trials were not dissociated in either the ERP or time-frequency analyses.

One-way ANOVA with "Intervention" (Real versus Sham) as a within-subjects factor were conducted to compare all measures of the ERN and Pe at Real relative to Sham stimulation. Given that MF theta is oscillatory activity is not only seen on error trials, two-way repeated measures ANOVA were used to test for the presence of a tDCS-induced effect on MF theta and occipital alpha, with "Intervention" (Real versus Sham) and "Trial-type" (Standard Go-trials versus Aware error trials) as within-subjects factors. Between-subject bivariate correlation analyses (Pearson's *r*) were used to examine the relationship between tDCS-related changes in the EEG signal dynamics at the per-subject average single-trial level and tDCS-related changes in behaviour (error awareness for Repeat No-go trials and Overall Mean Awareness RT). Despite collapsing across Repeat and Stroop No-go trials for the EEG analyses, it was elected not to collapse across Repeat and Stroop No-go trials for the behavioural measure of error awareness, since a tDCS-related change in error awareness was only manifest for Repeat No-go trials. Because these correlation analyses were motivated by the evidence accumulation account of error awareness, which provides strong

directional hypotheses regarding the relationships between the dynamics of decision variables and evidence signals and behaviour, one-tailed tests were used. All analyses conducted on data collected during the Online blocks were also applied to the data collected during the Offline blocks.

6.3 Results

Impact of tDCS on behaviour for full sample of participants

Behavioural performance on the EAT for the full sample of participants during Online and Offline tDCS is summarised in **Tables 6.1** and **6.2**, respectively.

Online. There was a main effect of Intervention on Overall Error Awareness ($F(1,27) = 5.34$, $p = .029$). An Intervention X No-go trial type interaction was also observed ($F(1,27) = 6.05$, $p = .021$), and paired sample t-tests indicated that the interaction was driven by a tDCS-induced improvement in Error Awareness for Repeat No-go trials ($t(27) = 2.88$, $p = .007$, $d = 0.47$) which was absent for Stroop No-go trials ($p = .7$, $d = 0.11$). There was also a significant main effect of Intervention on Mean Awareness RT ($F(1,27) = 4.3$, $p = .048$), but there was no Intervention X No-go trial type interaction ($p = .6$). There were no main effects or interactions for Accuracy, Mean Awareness RT CV or Go-trial RT (all $F<1$). Therefore, consistent with the results of Chapter 5, Online tDCS over right dlPFC was associated with a specific improvement in error awareness for Repeat No-go trials, and faster awareness response times that were not specific to Repeat or Stroop No-go trials.

As was observed in Chapter 5, there were main effects of No-go trial type for both error awareness ($F(1,27) = 32.21$, $p < .001$) and Accuracy ($F(1,27) = 35.83$, $p < .001$). The former reflected greater Error Awareness for Stroop compared to Repeat No-go trials across both Real and Sham sessions, while the latter reflected significantly greater Accuracy for Repeat compared Stroop No-go trials across both Real and Sham sessions. Both these main effects were observed in all three of the other iterations of the behavioural analyses below.

Table 6.1. Performance on the EAT for Online Real and Sham stimulation: mean (SD)

	Real Stimulation	Sham Stimulation
Repeat Accuracy (%)	67.6 (18.9)	67.4 (20.4)
Stroop Accuracy (%)	51.2 (17.5)	54.4 (19.1)
Repeat Awareness (%)**	65.2 (26.7)	52.1 (25.7)
Stroop Awareness (%)	86.1 (10.8)	84.7 (12.8)
Mean Repeat Awareness RT (ms)	642.7 (94.6)	701.9 (146.1)
Mean Stroop Awareness RT (ms)	646.9 (114.1)	679.7 (105.2)
Mean Repeat Awareness RT CV (ms)	.24 (.1)	.26 (.1)
Mean Stroop Awareness RT CV (ms)	.27 (.1)	.29 (.1)

** $p<.01$

Table 6.2. Performance on the EAT for Offline Real and Sham stimulation: mean (SD)

	Real Stimulation	Sham Stimulation
Repeat Accuracy (%)	71.3 (14.9)	66.5 (18.9)
Stroop Accuracy (%)	54.6 (14.7)	55.6 (20.1)
Repeat Awareness (%)**	63.3 (22.1)	50.7 (23.7)
Stroop Awareness (%)	87.8 (13.9)	87.4 (10.1)
Mean Repeat Awareness RT (ms)	690.3 (140.3)	696.2 (142.1)
Mean Stroop Awareness RT (ms)	644.1 (136.1)	679.5 (125.8)
Mean Repeat Awareness RT CV (ms)	.24 (.1)	.20 (.1)
Mean Stroop Awareness RT CV (ms)	.26 (.1)	.26 (.1)

**** $p<.01$**

Offline. The pattern of results for the behavioural data acquired post-stimulation was highly comparable with that observed for the behaviour acquired during stimulation, aside from the absence of a main effect of Intervention on Mean Awareness RT. There was a main effect of Intervention on Overall Error Awareness ($F(1,26) = 4.1$, $p = .043$), and there was a significant Intervention X No-go trial type interaction ($F(1,26) = 4.39$, $p = .038$). Paired sample t-tests indicated that the interaction was driven by a tDCS-induced improvement in Error Awareness for Repeat No-go trials ($t(26) = 2.42$, $p = .022$, $d = .53$) which was not present for Stroop No-go trials ($p = .75$, $d = .12$). There were no main effects of Intervention or Intervention X No-go trial type interactions for Accuracy, Mean Awareness RT, or Mean Awareness RT CV or mean Go-trial RT (all $F < 1$). Therefore, tDCS over right dlPFC was also associated with a specific improvement in Error Awareness for Repeat No-go trials that lasted for at least a ~26 minutes following stimulation.

There was a significant association between the tDCS-related change in Error Awareness for Repeat No-go trials during Online and Offline ($r = .54$, $p = .003$), and despite the absence of a main effect of Intervention on Mean Awareness RT for Offline, there was a positive correspondence between the tDCS-related change in Mean Awareness RT during Online and Offline ($r = .380$, $p = .051$).

As was observed for experiments 1 and 4 in Chapter 5, there was substantial variability across individuals in terms of their response to tDCS (**see Figure 6.2**), including a number of participants for whom there was either no change, or deterioration, in Error Awareness for Repeat No-go trials, with Real stimulation.

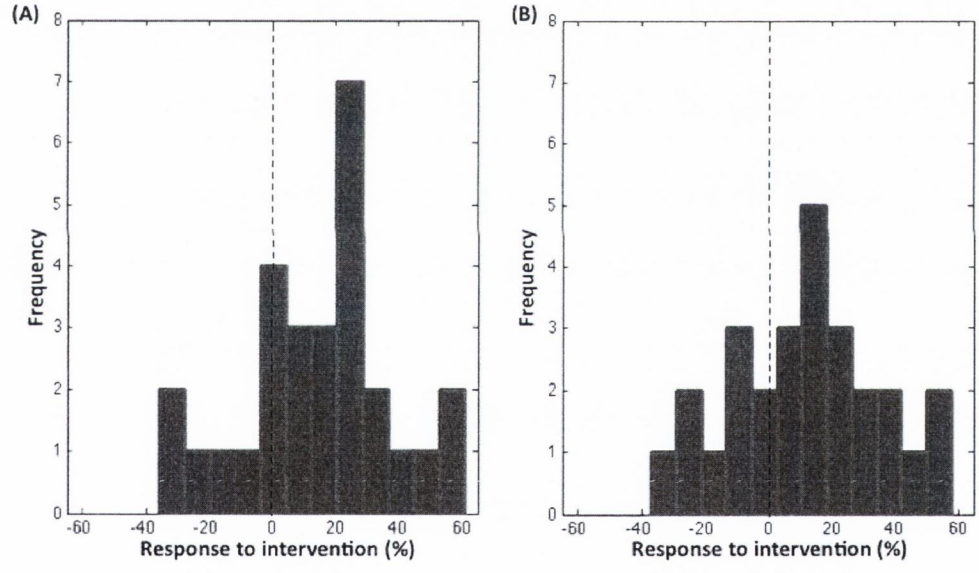

Figure 6.2 Inter-individual variability in response to intervention for Online and Offline tDCS. Histograms displaying individual variability in response to the intervention for Online (A) and Offline (B) tDCS. As in Chapter 5, response to the intervention was defined as each participant's mean difference score between percentage Error Awareness for Repeat No-go trials at Real versus Sham stimulation conditions. Positive values indicate better Error Awareness for Repeat No-go trials at Real compared with Sham stimulation.

Impact of tDCS on behaviour for EEG sub-group

Due to the fact that a smaller sample was available for the EEG analyses, the above analyses were repeated on this EEG sub-group to verify that they demonstrated behavioural patterns that were representative of the group as a whole. The associated results for Online and Offline tDCS are summarised in **Tables 6.3** and **6.4**, respectively.

Online. There was no main effect of tDCS on Overall Error Awareness (p = .2, d = .38), but there was a significant Intervention X No-go trial type interaction ($F(1,17)$ = 6.65, p = .02). Paired sample t-tests indicated that the interaction was driven by a tDCS-induced improvement in Error Awareness for Repeat No-go trials (t(17) = 2.12, p =.049, d = .5) which was absent for Stroop No-go trials (p = .32, d = -.13). A significant main effect of Intervention on Mean Awareness RT was observed ($F(1,17)$ = 12.63, p = .002), but there was no Intervention X No-go trial type interaction (p = .11). There were no main effects of Intervention or Intervention X No-go trial type interactions for Accuracy, Mean Awareness RT CV, or mean Go-trial RT (all p > .05). Thus, the Online tDCS-induced improvements in Error Awareness for Repeat No-go trials and Overall Mean Awareness RT were also apparent in the EEG sub-group.

Offline. For offline tDCS with the EEG sub-group, there was no main effect of Intervention on Error Awareness ($F(1,15)$ = 4.63, p = .058), no Intervention X No-go trial type interaction (p > .1). For this condition, Go-trial RT was not normally distributed for either real or sham tDCS. This variable was therefore subjected to a reciprocal transformation to improve the skew of the distribution. There were no main effects of Intervention or Intervention X No-go trial type interactions for mean Go-trial RT, Accuracy, Mean Awareness RT, or Mean Awareness RT CV (all F < 1).

Table 6.3. Performance indices on the EAT for Online Real and Sham stimulation in the EEG sub-group: mean (SD)

	Real Stimulation	Sham Stimulation
Repeat Accuracy (%)	66.1 (16.4)	65.3 (19.2)
Stroop Accuracy (%)	49.7 (14.3)	50.4 (18.1)
Repeat Awareness (%)**	66.5 (25.3)	53.1 (27.1)
Stroop Awareness (%)	85.1 (8.7)	87.5 (7.3)
Mean Repeat Awareness RT (ms)	635.8 (102.1)	734.3 (128.1)
Mean Stroop Awareness RT (ms)	640.6 (109.8)	686.7 (100.7)
Mean Repeat Awareness RT CV (ms)	.24 (.1)	.26 (.1)
Mean Stroop Awareness RT CV (ms)	.29 (.1)	.27 (.1)

** p<.01

Table 6.4. Performance indices on the EAT for Offline Real and Sham stimulation in the EEG sub-group: mean (SD)

	Real Stimulation	Sham Stimulation
Repeat Accuracy (%)	64.4 (13.8)	66.7 (19.3)
Stroop Accuracy (%)	49.2 (13.1)	52.3 (19.9)
Repeat Awareness (%)**	63.8 (28.3)	50.3 (24.8)
Stroop Awareness (%)	87.8 (9.8)	88.6 (11.6)
Mean Repeat Awareness RT (ms)	636.7 (125.1)	678.6 (124.7)
Mean Stroop Awareness RT (ms)	572.2 (115.3)	647.8 (89.6)
Mean Repeat Awareness RT CV (ms)	.27 (.2)	.22 (.1)
Mean Stroop Awareness RT CV (ms)	.29 (.1)	.26 (.1)

** $p<.01$

Impact of tDCS on the ERN and Pe components

Online. There was no main effect of Intervention on either the amplitude ($p = .27$) or the peak latency of the ERN ($p = .38$). There was also no main effect of Intervention on Pe amplitude ($p = .53$), but Real stimulation was associated with a significantly faster build-up rate ($F(1,17) = 6.54$, $p = .02$), and an earlier peak latency ($F(1,17) = 8.06$, $p = .011$) of the Pe relative to the Sham condition (**Figure 6.3**). This pattern of results for the Pe was also apparent when the per-subject average single-trial measures were analysed: There was no main effect of Intervention on amplitude ($p = .3$), whereas Real stimulation was associated with a significantly faster build-up rate ($F(1,17) = 4.49$, $p = .049$), and an earlier peak latency ($F(1,17) = 7.18$, $p = .016$) relative to Sham.

Between-subject bivariate correlation analyses (one-tailed test with alpha threshold at $p = 0.1$) were conducted using the per-subject average single-trial measures to examine the relationships between tDCS induced changes in the dynamics of the Pe and the tDCS induced changes in behaviour. Significant associations between the tDCS-related change in peak latency and the tDCS-related change in Mean Awareness RT ($r = .46$, $p = .056$), and the tDCS-related change in Error Awareness for Repeat No-go trials ($r = .422$, $p = .081$) were observed. There was also a significant association between the tDCS-related change in build-up rate and the tDCS-related change in Mean Awareness RT ($r = -.469$, $p = .05$), but not with the change in Error Awareness for Repeat No-go trials ($p = .141$).

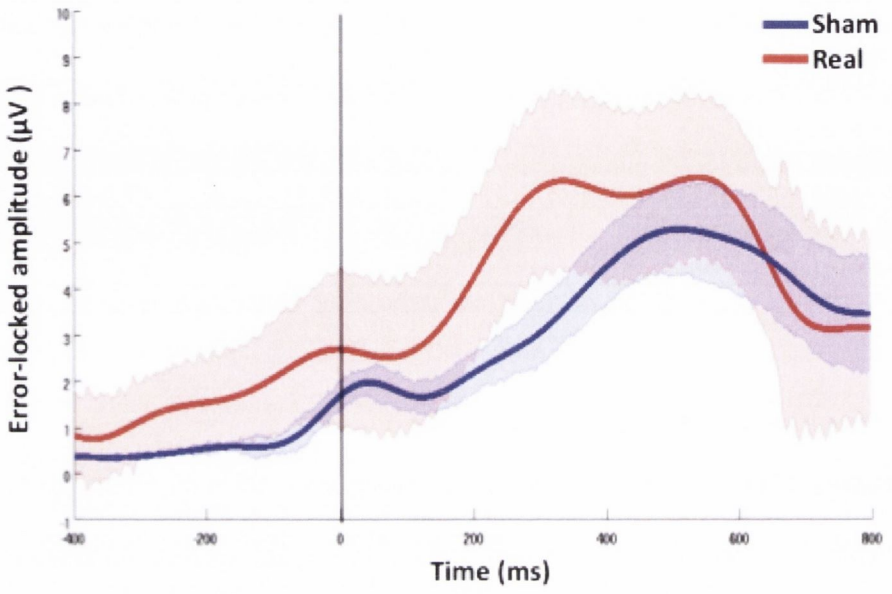

Figure 6.3 The grand-average error positivity for Online Real and Sham stimulation. Error-locked error-positivity (Pe) waveforms for Real and Sham stimulation. Real, compared to sham, stimulation was associated with a significantly steeper build-up and earlier peak latency of the Pe.

Offline. With respect to the EEG data recorded after tDCS, there was no main effect of Intervention on either the amplitude (p = .36) or the peak latency of the ERN (p = .76). For the Pe, there was no difference between Real and Sham for amplitude (p = .31), or peak latency (p = .28), but again Real stimulation was associated with a significantly faster build-up rate ($F(1,15) = 6.48$, p = .022) of the Pe relative to the Sham condition (**Figure 6.4**). At the single-trial level, there was no main effect of Intervention on amplitude (p = .35**),** but Real stimulation was associated with non-significant trends towards a faster build-up rate ($F(1,15) = 3.73$, p = .073), and an earlier peak latency ($F(1,15) = 4.1$, p = .061), relative to Sham.

With regard to the between-subject correlation analyses (one-tailed), a significant association between the tDCS-related change in Pe peak latency and the tDCS-related change in Mean Awareness RT was observed (r = .46, p = .072). However no other

relationships between the tDCS induced changes in the dynamics of the Pe and the tDCS induced changes in behaviour were significant (all $p > .2$).

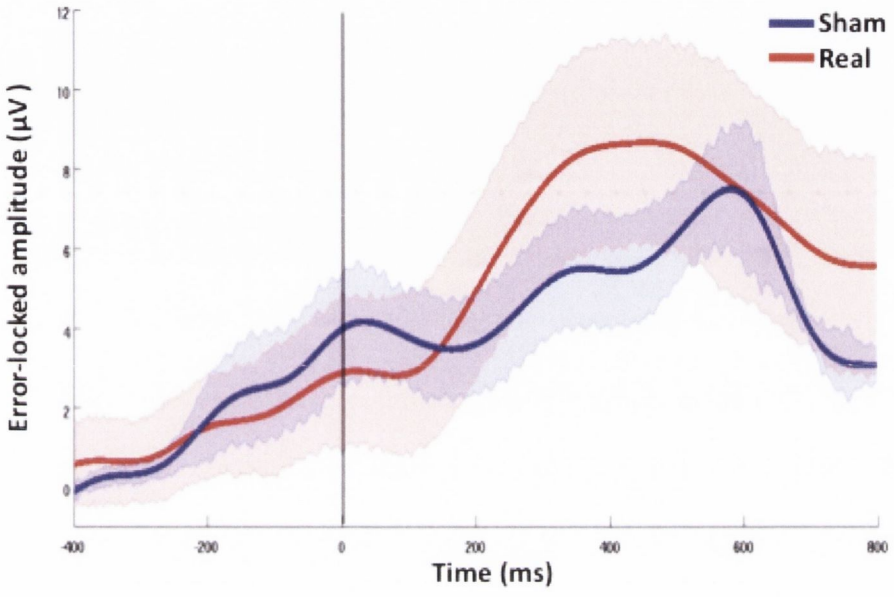

Figure 6.4 The grand-average error positivity for Offline Real and Sham stimulation. Error-locked error positivity (Pe) waveforms for Real and Sham stimulation. Real, compared to sham, stimulation was associated with a significantly steeper build-up of the Pe .

Impact of tDCS on MF theta and Occipital Alpha

Online. For Online tDCS there was a main effect of Intervention on response-locked MF theta ($F(1,17) = 4.54$, $p = .048$), but there was no Intervention X Trial-type interaction ($p = .365$; see **Figure 4.4**). Therefore, Real compared to Sham tDCS was associated with an increase in response-locked MF theta for both Standard Go-trials and Aware error trials.

There was also a significant main effect of Trial-type ($F(1,17) = 32.59$, $p < .001$), indicating that, consistent with previous findings (Chapter 3; Murphy et al., under review), Aware error trials evoked a greater MF theta response relative to Standard Go-trials across both Real and Sham conditions. For response-locked occipital alpha power, there was no main effect of either Intervention ($p = .204$) or Trial-type ($p = .087$), and no Intervention X Trial-type interaction ($p = .683$). Therefore, tDCS was not associated with a generic enhancement of oscillatory activity across all frequency bands.

Between-subject correlations (one-tailed) using the per-subject average single-trial measures of MF theta power were conducted to examine the relationships between tDCS induced changes in MF theta and the tDCS induced changes in behaviour. Significant associations were observed between the tDCS-related change in MF theta for Standard Go-trials and both the tDCS-related change in Mean Awareness RT (r = -.46, p = .056) and the tDCS-related change in Error Awareness for Repeat No-go trials (r = .46, p = .058). Similarly, the tDCS-related change in MF theta for Aware error trials was significantly associated with the tDCS-related change in Mean Awareness RT (r = -.47, p = .047), and Error Awareness for Repeat No-go trials (r = .46, p = .055).

Offline. For Offline tDCS, there was a non-significant trend toward a main effect of Intervention on MF theta power ($F(1,15) = 3.45$, p = .083), but no Intervention X Trial-type interaction (p = .425), reflecting a numerical increase in MF theta for both Standard Go-trials and Aware error trials for Real stimulation relative to Sham. Again, there was significant main effect of Trial-type ($F(1,17) = 14.38$, p = .002), reflecting greater MF theta for Aware error trials relative to Standard Go-trials, irrespective of stimulation condition. For response-locked occipital alpha power, there was no main effect of either Intervention (p = .312) or Trial-type (p = .554), and no Intervention X Trial-type interaction (p = .655).

With regard to the between-subject correlation analyses, there were no significant associations between the tDCS-related changes in MF theta and behaviour for either Standard Go-trials or Aware error trials (all $p > .2$).

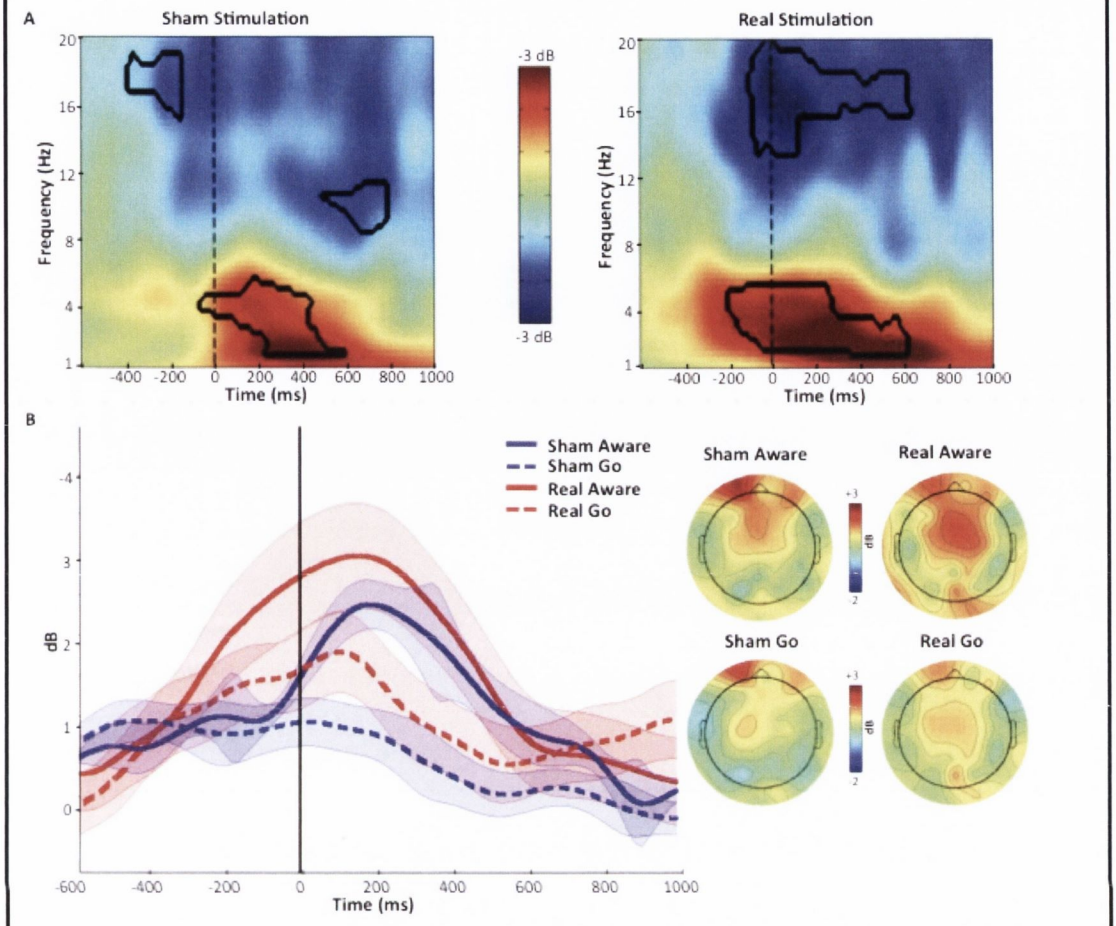

Figure 6.5 Response-locked medial frontal theta for Online Real and Sham stimulation. (A) Response-locked time-frequency plots of medial frontal (MF) power, for Real and Sham stimulation, averaged across Aware error and Standard Go trials. Black lines encircle regions of significance ($p < 0.01$, paired-samples t-test) relative to a pre-stimulus baseline (300 ms prior to stimulus onset). **(B)** Grand-average temporal evolution of response-locked MF theta (2-7 Hz) waveforms spit by trial-type for each condition. Real stimulation was associated with an increase in response-locked MF theta for both Standard Go-trials and Aware error trials, relative to Sham stimulation. Spatial topographies show distribution of associated activity for Aware error and Standard Go trials in the upper and lower rows, respectively. Shaded error bars = s.e.m.

6.4 Discussion

The main aims of the present chapter were to interrogate the electrophysiological basis of older adults' gains in error awareness when anodal tDCS is applied over right

dlPFC, and to determine whether these gains persist beyond the stimulation period. Firstly, consistent with the findings in Chapter 5, anodal tDCS over right dlPFC was associated with an improvement in error awareness for Repeat No-go trials during stimulation, which again, could not be attributed to changes in accuracy or slowed response times. This constitutes the third demonstration of this effect, with comparable effect sizes in each experiment (Cohen's *d* has chronologically emerged as 0.51, 0.42 and 0.47), indicating that this is a robust and reproducible effect. This improvement in error awareness for Repeat No-go trials (Cohen's *d* = .53) was also evident beyond the termination of the stimulation, further underlining the promise of this approach for remediating awareness deficits. As predicted, at the electrophysiological level, the tDCS related improvements in error awareness were associated with enhanced MF theta power, as well as both a steeper build up and earlier peak of the Pe. Some of the effects did not extend to the post-stimulation period, but as will be discussed below, this may not necessarily be evidence for a weakening of the effect upon the termination of stimulation.

Online effects of tDCS on electrophysiology

A tDCS related increase in MF theta oscillatory power was observed for both Aware and Standard Go-trials. This observation is consistent with the original hypothesis that tDCS over right dlPFC would be associated with secondary modulation of neural activity in the pMFC. This finding provides novel evidence for an intimate relationship between these regions in mediating error awareness, and performance monitoring, in general. This will be discussed further below (see *The role of pMFC and right dlPFC in error awareness*). Significant relationships between the tDCS related gains in MF theta and the tDCS related gains in both rates of error awareness and speed of awareness response times were observed, lending further credence to the notion that the quantity encoded by MF theta oscillations provides critical input to the error detection process. However, the enhancement in MF theta was not confined to error trials but was equally prevalent on Standard Go-trials, indicating that, as suggested in Chapter 5, the up-regulation of right dlPFC may facilitate adaptive neural activity in a proactive and sustained manner. This in turn may point to the potential of tDCS to produce gains in other performance monitoring and cognitive control processes which do not necessarily apply to error detection but have also been associated with theta oscillations in the medial frontal cortex (Cavanagh et al., 2012; Cohen & Cavanagh, 2011; Kahana, Seelig, & Madsen, 2001; Nigbur, Ivanova, & Stürmer, 2011; Van de Vijver et al., 2014).

Similarly, tDCS resulted in a steeper rate of rise, and an earlier peak, of the Pe, and these changes were correlated with the observed improvements in error awareness and error signalling response times. These changes in the dynamics of the Pe indicate that tDCS increased the rate at which the evidence bearing on the error detection decision process was accumulated. Extrapolating from the discussion in Chapter 3, wherein it was proposed that the age-related declines at the evidence accumulation stage were likely due to reduced availability of error evidence, the tDCS related gains in evidence accumulation in the present study are likely the product of enhanced MF theta oscillatory power. However, the possibility that tDCS had a dissociable impact on the accumulation process should be given due consideration in future research, as should the possibility that tDCS influenced regions mediating other putative sources of error evidence, such as proprioceptive feedback from the erroneous response or interoception of autonomic responses accompanying the error (Ullsperger et al., 2010; Wessel et al., 2011).

Offline effects of tDCS on behaviour and electrophysiology

While the Online effects of tDCS on both behaviour and electrophysiology are of substantial theoretical importance, the translational potential of these findings is largely contingent on the capacity for tDCS to produce prolonged changes in error awareness. Encouragingly, previous studies have shown that multiple consecutive sessions of anodal tDCS can induce gains in cognitive functioning that persist for several weeks (Boggio et al., 2012; Doruk et al., 2014; Joen & Han, 2012). For instance, Doruk et al. (2014) showed that in a sample of Parkinson's disease patients, who received ten consecutive sessions of anodal stimulation to either left or right dlPFC, improvements in performance on a measure of executive functioning, known as the Trail Making Test B, were still evident at a 1-month follow-up. It was not within the scope of the present thesis to administer multiple sessions or examine the long-term effects with follow-up testing sessions. The present study did however provide the opportunity to investigate whether there was evidence for short-term after-effects within the ~26 minutes following the termination of tDCS.

Firstly, with respect to behaviour, the tDCS related increase in error awareness for Repeat No-go trials was also apparent for the Offline blocks of the EAT, and there was a significant correspondence between the magnitude of these gains (12.6%) and the gains observed for the Online blocks (13.1%). The significant effect of tDCS on mean awareness response times that was observed for the Online blocks was not evident for the Offline blocks, however. Further, in the sub-set of participants who provided sufficient aware error trials to facilitate analysis of their EEG, the effect of tDCS related gains in error awareness

for Repeat No-go trials was reduced to a non-significant trend. At face value, these behavioural findings would seem to imply that the effect of tDCS diminishes upon the termination of stimulation.

As regards the electrophysiological effects, there were some discrepancies between what was observed at the trial-averaged and single-trial levels of analysis for the Pe. At the trial-averaged level, consistent with the Online blocks, tDCS was associated with a steeper rate of rise of the Pe, but unlike in the Online blocks there was no difference in peak latency between the two conditions. At the single-trial level, the same pattern of effects of tDCS on rate of rise and peak latency of the Pe that were observed for Online were observed for Offline, but they did not reach the conventional level of significance. Similarly, the effect of tDCS on MF theta power was limited to a non-significant trend for greater MF theta power on Standard Go-trial at Real compared to Sham stimulation.

Taken together, these behavioural and electrophysiological findings may point to a weakening of the tDCS effect beyond the immediate stimulation period, however it is also possible that there was insufficient statistical power to detect some of the effects in the Offline analysis due to a diminished trial count. Owing to concerns that the participants may have found it difficult to endure a longer testing session, only three blocks of the EAT were administered post-stimulation. The associated reduction in potential error trials, compounded with the loss of several participants that did not provide enough aware error trials following artifact rejection, would have resulted in markedly reduced statistical power for the Offline analyses. The capacity to detect effects in the Offline blocks, if present, may be enhanced via the implementation of data transformation methods to improve the signal-to-noise ratio of individual trials (cf. Kelly & O'Connell, 2013; Parra, Alvino, Tang et al., 2002; Steinhauser & Yeung, 2010).

Either way, the fact that there were any effects at all on error awareness and two electrophysiological signals that are tightly related to error awareness post-stimulation, would appear to implicate LTP-like activity (e.g. Venkatakrishnan & Sandrini, 2012), which theoretically should be a good indicator of the potential of this tDCS montage to induce enduring plastic changes in the neural systems underlying error awareness. The extent to which these changes would confer benefits to everyday life represents another question in itself, but the knowledge that performance on the EAT is representative of awareness on real-world tasks (Chapter 2) may also suggest promise in this regard.

The role of pMFC and right dlPFC in error awareness

The evidence for a causal relationship between the right dlPFC and pMFC regions in enhancing error awareness calls for renewed consideration of how these regions might interact to mediate error awareness. As discussed in Chapter 1, it is broadly assumed that the pMFC monitors performance for errors/negative action outcomes/salient events and signals the need for other regions such as the lPFC to regulate cognitive control to achieve optimal behavioural outcomes. Within this broad perspective, several authors have emphasised the role of response conflict or an internal response comparison as critical determinants of the pMFC error signal (Cohen, 2014; Steinhauser & Yeung, 2008; Yeung et al., 2004). For instance, in a recent review, Cohen (2014) highlighted how during response conflict, which he defines as competition between two or more conflicting actions when a mistake could be made, pMFC generated MF theta oscillations are invariably observed. This notion that two different responses may be activated simultaneously is directly reconcilable with sequential sampling models of decision-making, wherein evidence is being accumulated separately for two alternative choices. In the case of first-order performance on paradigms such as the EAT, there would be separate competing accumulators for the response options of executing a button press versus withholding a button press. Instances where both accumulators get close to their threshold, but one ultimately wins out, would supposedly evoke levels of post-response conflict proportionate to the likelihood that the wrong choice was made, and accordingly serve as an error evidence signal for the second-order decision.

In Chapter 1 it was proposed that unaware errors on the EAT are precipitated by attentional lapses, which compromise the representation of the appropriate stimulus-response mapping rules. Such lapses could conceivably result in a failure to initiate the accumulation of evidence corresponding to the correct response option of withholding a button press. The accumulator representing the pre-potent response option of executing a button press would accordingly reach its threshold, and, in the absence of a competing accumulator for withholding a button press, there would be insufficient post-response conflict to inform the error awareness decision process. Alongside its role in implementing cognitive control to resolve response conflict and facilitate remedial actions, the lPFC, particularly the dorsal region, has also been heavily implicated in the maintenance and manipulation of task-relevant information (Goldman-Rakic, 1996; Koechlin & Summerfield, 2007; Zysset, Müller, Lohmann, & von Cramon, 2001). Anodal stimulation of the dlPFC may therefore enhance the capacity of the region to maintain an accurate representation of the appropriate

response, which, in instances where an error response is made, contributes to post-response conflict that is encoded by MF theta.

One caveat of this interpretation it that there does not appear to be any evidence to support a hemispheric lateralisation of function with respect to the role of the dlPFC in the maintenance and manipulation of task relevant information. On the other hand, numerous fMRI, PET and lesion studies have indicated that the capacity for sustained attention, defined as the ability to maintain an alert, goal-directed focus in the absence of exogenous stimulation (Robertson & Garavan, 2004) relies on a predominantly right lateralised fronto-parietal network, including the right dlPFC (Corbetta & Shulman, 2002; Coull et al., 1998; Posner & Peterson, 1990; Sturm & Willmes, 2001; Weissman, Roberts, Visscher, & Woldorf, 2006). Robertson and Garavan (2004) have further proposed that the right dlPFC component of the network may have a specific "executive" role in the self-sustained innervation of the sustained attention system. The capacities for sustained attention and error awareness were found to correlate positively across individuals in Chapter 2, as well as in a number of other earlier studies (Hoerold et al., 2008; McAvinue et al., 2005; O'Keeffe et al., 2007). Both sustained attention (Greene, Bellgrove, Gill, & Robertson, 2009; Grefkes, Wang, Eickhoff, & Fink, 2009) and error awareness (Hester et al., 2012) are selectively sensitive to noradrenergic modulation. Further, the right dlPFC is one of the regions most consistently implicated in the literature on awareness deficits in clinical populations (Chapter 1). These neuroimaging, behavioural, pharmacological, and clinical findings, along with the tDCS findings of the present thesis, converge to support the idea that the right dlPFC may facilitate error awareness through its role in maintaining an alert and goal-directed focus (Robertson, 2010). This hypothesis is furthermore consistent with prior demonstrations of age-related deficits in sustained attention (Bunce, 2001; Davies & Davies, 1975; McAvinue et al., 2012; Mouloua & Parasuraman, 1995). Accordingly, it is conceivable that up-regulation of the right dlPFC via anodal tDCS reduces the frequency of attentional lapses which would otherwise compromise the representations of the appropriate stimulus-mapping rules, which, as discussed above, are integral to driving the post-response conflict/MF theta oscillatory activity which feeds into the error awareness decision process.

Methodological Considerations

Given that the electrode montage and stimulation parameters employed in the present chapter were the same as those implemented in experiments 5.1 and 5.4 of Chapter 5, it is possible to exclude at least two factors that may have otherwise constrained the interpretation of the present findings. Namely, it is possible to rule out the potential roles of

reference electrode over the vertex, and expectancy effects relating to the induced somatic sensations, in driving the effects on error awareness. The primary limitation of the present study concerns the potentially insufficient statistical power for some of the analyses, in particular for the Offline blocks. In addition, due to inadequate numbers of unaware error trials following artifact rejection, it was not possible to compare the electrophysiological correlates of unaware errors across Real and Sham tDCS. It would be interesting for future work to determine whether the capacity of the MF theta and Pe signals to discriminate aware from unaware error trials is affected by tDCS. Furthermore, although it was determined that tDCS was not associated with a generic enhancement of oscillatory activity across all frequency bands, future work should aim to further clarify the specificity of the MF theta effect by comparing all other frequency bands in the peri-response time window across Real and Sham conditions. Future work should also determine whether electrophysiological indices of sustained attention, such as *pre-stimulus* parietal alpha (Dockree, Kelly, Foxe et al., 2007; O'Connell, Dockree, Robertson et al., 2009) are modulated in a manner that would be consistent with the (above) implication of sustained attention processes.

Conclusions

Combining tDCS with EEG provided the opportunity to investigate the electrophysiological correlates of tDCS induced behavioural improvements in error awareness. Enhancements in two electrophysiological signals that are related to evidence encoding and evidence accumulation, pMFC generated MF theta power and the Pe, for the error awareness decision process were observed. These findings provide novel evidence for a causal relationship between the pMFC and right dlPFC in mediating error awareness, and accordingly represent an important step towards a better understanding of the mechanisms involved in tDCS induced improvements of error awareness. Persistence of the effects beyond the immediate stimulation period were additionally observed, suggesting that these findings may be of clinical importance.

Chapter 7: General Discussion

7.1 The capacity for error awareness in healthy older adults

7.1.1 Contributions

One of the strongest themes to emerge from the extensive literature on cognitive ageing is that capacities which rely on cognitive control and frontal lobe structures are disproportionately affected by increasing age. Converging evidence from longitudinal (Nyberg et al., 2010) and cross-sectional (Calin et al., 2007; Cherry & Hellige, 1999; Clark & Knowles, 1973; Brickman et al., 2006, Lu et al., 2011) studies furthermore suggests greater age-related decline in right over left hemisphere functioning. In parallel, research on anosognosia that cuts across diverse clinical populations, has consistently indicated that compromised functioning of the frontal lobe, particularly the right frontal lobe, leads to an increased risk for impaired awareness of cognitive abilities. Despite these overlapping neural substrates, the impact of aging on metacognition has received surprisingly little attention in the literature. As detailed in Chapter 1 a small number of studies have suggested that older adults demonstrate a diminished ability to monitor and appraise cognitive performance (Bruce, Coyne, & Botwinick, 1982; Graham, Kunik, Doody, & Snow, 2005; Rabbitt, 1990; Suchy, Kraybill, Frnachow, et al., 2011), but others have provided evidence to the contrary (Clare, Whitaker, & Nelis, 2010; Lovelace & Marsh, 1985; Rabbitt, 2002, Ries et al., 2012). Overall, drawing firm conclusions about the integrity of metacognitive abilities in older adults based on this research is difficult not only because of the inconsistent findings across studies, but also because of the failure to control for factors such as speed of processing, accuracy of primary task performance, pathology-related cognitive impairments, as well as the potential for domain-specific impairments.

Chapter 2 employed a multi-domain assessment of self-awareness in healthy older adults and young adult controls that was tailored to overcome many of the limitations of previous research. Convergent data from a laboratory measure of online error awareness and real-world measures of awareness of attentional control and memory functioning indicated that older adults have significantly reduced awareness of cognitive functioning, relative to young adults. These group differences could not be attributed to speed of cognitive response, speed of motor response, anxiety, depression or pathology-related impairments. Furthermore, there was a significant correspondence between the age-related deficits in online error awareness, which could not be attributed to group differences in the accuracy of primary task performance, and awareness of attentional control and awareness of memory functioning.

Separate lines of empirical work had previously demonstrated that clinical populations such as TBI, schizophrenia, dementia, and FTD which frequently present with deficits in self-awareness (Bivona et al., 2008; Hart et al., 2004; Karnath & Baier, 2010; Neary et al., 1998; Shad et al., 2004; Wild & Cotrell, 2003) also exhibit deficits in online awareness of errors (Brazil et al., 2009; Carter et al., 2001; Giovannetti, Libon, & Hart, 2002; Hart et al., 1998; McAvinue et al., 2005; O'Keeffe et al., 2007), but there had been no empirical support for a relationship between these deficits before now. Although it has yet to be established if this relationship is causal in nature, there is now basis for proposing that in addition to online error awareness being important for remedial actions following errors in the short-term (Betcher & Giovannetti, 2009; Klein et al., 2007; Nieuwenhuis, et al., 2001; Wessel et al., 2011), the capacity for error awareness may also have implications for the accuracy with which individuals appraise their cognitive abilities in the longer term (Robertson, 2010). Specifically, as a result of having a tendency to miss lapses and errors during moment-to-moment performance, individuals may not recognise the need to update their self-concept in accordance with disease-related deterioration of their cognitive abilities, or the onset of cognitive senescence. No association was observed between online error awareness and awareness of socio-emotional functioning. But, given that awareness of socio-emotional functioning appeared to be unaffected by ageing, it is likely that the representations that older adults had of themselves in their younger years with respect to this domain, remain accurate into late life, independent of the capacity to self-monitor and other domains of cognitive functioning.

This evidence of a significant age-related reduction in self awareness is particularly significant in light of the associations that have been documented between impaired awareness of deficits and a range of unfavourable outcomes, including engagement in risky behaviour (Cotrell & Wild, 1999; Starkstein et al., 2007), increased care-giver burden

(Seltzer et al., 1997), poor motivation for treatment (Fleming et al., 1996; Malec & Moessner, 2001) and poor general prognosis (David, 1992; McEvoy et al., 1989). Accordingly, it was concluded that there is a strong imperative for research to elucidate the neural basis of error awareness deficits, and to make use of this knowledge to develop targeted interventions.

Heeding this, Chapter 3 focussed on elucidating the electrophysiological basis of error awareness in older adults and young adult controls. The noted association between online error awareness and measures of awareness in daily life in Chapter 1 served to support the error awareness task (EAT) as an objective and ecologically valid measure of awareness, which accordingly provided justification for employing it again in Chapter 2, as well as in the subsequent empirical work within the thesis. Previous work had reported that error-related EEG components, medial frontal (MF) theta, the error-related negativity (ERN) and the error positivity (Pe), were attenuated in older age, but no EEG study had explicitly measured error awareness in healthy older adults. Thus, it was not clear from these studies whether the reduction in these components was due to diminished rates of error awareness or an age-related attenuation in electrophysiological response that would also be evident when aware error trials were analysed in isolation. Further, it has recently been demonstrated that the peak latency and amplitude of the Pe, is more closely locked to the timing of the awareness response than to the timing of error commission (Murphy et al., 2012). Thus attenuation of the error-aligned Pe could also be attributable to greater variability in the timing of the emergence of awareness, as opposed to failures of awareness. A related limitation of these studies was that they only measured the *averaged* amplitude of the Pe waveform, which fails to capture much of the inherent variability in component amplitude and latency that may be evident at the single-trial level (Bland et al., 2011; Debener et al., 2006; Eichele, et al., 2010).

Noting these limitations, and capitalising on the recently conceptualised mechanistic account of error awareness as a decision process (Steinhauser & Yeung, 2010; 2012; Murphy et al., 2012; Murphy et al., under review), Chapter 3 constituted a theory-driven interrogation of visual evoked potentials (VEPs), MF theta oscillatory power, the ERN and the Pe, and their relationship with behavioural measures of error awareness in older adults. Replicating the findings of Chapter 2, the behavioural data indicated that older adults were significantly less likely to be aware of their errors than young adult controls. At the electrophysiological level, it was found that the VEPs for aware errors did not differ from the VEPs for unaware errors, excluding the possibility that older adults error awareness deficits were the result of deficits in early sensory stimulus processing. On the other hand, consistent with predictions

of the evidence accumulation account of error awareness, as well as previous findings in young adults (Murphy et al., under review), the EEG data indicated that, older adults' MF theta and Pe signals predicted the timing and accuracy of their error signalling responses. At the same time, group comparisons revealed general age-related reductions in MF theta oscillatory power, as well as build-up rate and peak latency of the Pe. It was consequently reasoned that older adults error awareness deficits may be attributable to weaker pMFC generated error evidence. Further, the finding that an age-related reduction in MF theta power was evident across all trial types on the EAT is consistent with the notion that older adults may have a deficit in performance monitoring that does not uniquely impact on their capacity to consciously detect performance errors (e.g. Anguera et al., 2013; van de Vijver et al., 2014).

From a methodological point of view, Chapter 3 also demonstrated that in addition to the trial-averaged error-aligned Pe being sensitive to jitter in the timing of error awareness (Murphy et al., 2012), the amplitude of the trial-averaged awareness response-aligned Pe can be comparably affected by jitter in the preparation and execution of the motor response. Although analyses at the single-trial level did indicate that the attenuated amplitude in the trial-averaged Pe could not be fully explained by either source of variability at the post-error stage, the potential limitations of both trial-averaged methods of measurement nonetheless highlight the need for previous and future investigations of group differences in Pe morphology to verify that any Pe findings that are considered meaningful are also apparent at the single-trial level.

Chapter 4 reviewed the evidence that transcranial direct current stimulation (tDCS) may represent a valuable tool for a wide array of both scientific and clinical purposes. Subsequently, Chapter 5 employed tDCS with the dual goals of determining whether right dorsolateral prefrontal cortex (dlPFC) plays a causal role in supporting error awareness and assessing the potential of tDCS to remediate error awareness deficits in older age. The extent to which the data supported the latter will be discussed in a subsequent section (*The utility of tDCS as a tool for ameliorating error awareness*). The influence of electrode location (right vs left dlPFC) and current polarity (anodal vs cathodal) was tested in a series of separate single-blind, sham-controlled cross over experiments, each including 24 healthy older adults. Anodal tDCS over right, but not left, dlPFC was associated with a significant increase in error awareness for Repeat No-go trials, which could not be accounted for by changes in accuracy, slower response times, the neuromodulatory influence of the reference electrode, or expectancy effects due to greater somatic sensation. Nonetheless, given that the effect was highly variable across participants and the critical importance of reproducibility (Simons,

2014), it was deemed important to carry out a replication experiment of anodal tDCS applied over right dlPFC. The finding of a significant increase in error awareness for Repeat No-go trials was recapitulated, again with a comparable effect size (Cohen's d = .51 and .42, chronologically), indicating that the effect was reliable. Chapter 5 thus provided novel evidence to support the hypothesis that right lateralised dlPFC structures play a critical role in mediating awareness of cognitive functioning, which had been strongly suggested by the extensive literature on the clinical phenomenon of anosognosia.

Chapter 6 followed on directly from Chapter 5 by acquiring EEG data concurrent to tDCS and also investigating whether the effects of tDCS persisted beyond the stimulation period. The co-registration of EEG and tDCS provided both a window into the neurophysiological correlates of the tDCS-induced improvements in error awareness and a means to test the prediction that the application of tDCS over right dlPFC would be associated with neural network effects that involved secondary modulation of the pMFC. As predicted, this investigation revealed that the tDCS-induced improvements in error awareness were accompanied by enhanced MF theta power, in addition to both a steeper and earlier peak of the Pe.

This novel evidence for a causal relationship between right dlPFC and pMFC stimulated consideration of how these regions might interact to achieve error awareness, and consequently, what might fundamentally underpin older adults awareness deficits. As mentioned at several points throughout the thesis, response conflict is assumed to be a critical determinant of the pMFC error signal and the associated MF theta oscillations (Cohen, 2014; Steinhauser & Yeung, 2008; Yeung et al., 2004) which appear to provide an important source of evidence for the error awareness decision process (Murphy et al., under review). Levels of response conflict are understood to be directly related to the degree of competition between two or more conflicting response options (e.g. Cohen, 2014). This is compatible with the idea of evidence being accumulated separately in favour of two opposing choices in accumulation-to-bound models of decision-making. It has been suggested that the *margin* by which one accumulator wins by reaching its threshold would evoke levels of response conflict/MF theta proportionate to the probability that the wrong choice had been made, and would consequently serve as an evidence signal for the error awareness decision process. However, the extent to which response conflict would arise, or the accumulation of evidence for alternative response options would occur, would be contingent on the stable maintenance of an alert and goal directed state such that representations of the appropriate response are readily available. The right dlPFC has been heavily implicated as a critical neural substrate for this capacity (Corbetta & Shulman, 2002;

Coull et al., 1998; Posner & Peterson, 1990; Sturm & Willmes, 2001; Weissman et al, 2006). Instances where the right dlPFC is not sufficiently engaged are associated with attentional lapses (e.g. Weissman et al., 2006), which would conceivably result in the pre-potent response being executed without any competition to evoke sufficient levels of MF theta to inform the error awareness decision process. It has thus been reasoned that older adults awareness deficits may be fundamentally attributable to an increased propensity for attentional lapses (Bunce, 2001; Davies & Davies, 1975; McAvinue et al., 2012; Mouloua & Parasuraman, 1995) due to age-related deterioration of the right dlPFC (Calin et al., 2007; Cherry & Hellige, 1999; Brickman et al., 2006, Lu et al., 2011; Nyberg et al., 2010).

7.1.2 Limitations and Future directions

Given the exclusive reliance on the EAT as the measure of error awareness throughout the thesis, it is important to acknowledge that this paradigm is not without fault. Possibly one of its most conspicuous properties is its complexity. Task performance may arguably reflect the operations of a number of distinct component processes. For instance, it could be said that Repeat No-go trials place demands on working memory and Stroop No-go trials require more conflict processing. As pointed out in Chapter 1 a significant issue in studying error awareness is that laboratory tasks of error processing are typically characterised by very high levels of error awareness. The complex nature of the EAT thus serves the purpose of rendering the active maintenance of all rules at all times quite challenging, and consequently increasing the probability that the violation of a task rule may go unnoticed. Inducing unaware errors in this manner contrasts markedly with how unaware errors are typically elicited on the two other most common paradigms in error awareness research: tasks where participants are required to make judgements about perceptually degraded stimuli and oculomotor paradigms such as the anti-saccade task. In the former unaware errors are elicited by introducing high levels of uncertainty about which response is correct, and thus participants cannot always determine the accuracy of their response (Ullsperger et al., 2010). In the latter, while participants would usually have a high level of certainty about what response option is correct, erroneous saccades are often very fast and thus characterised by minimal sensory and proprioceptive feedback, and as such they may be uncertain about whether the correct response was actually executed. While these kinds of tasks may be more straightforward than the EAT, such strategic degradation of perceptual information does not provoke distinct types of unaware errors that frequently occur in real life (for example, those due to lapses of attention) which, critically, appear to be particularly pertinent to clinical populations that exhibit deficits in awareness of cognitive functioning

(e.g. Carter et al., 2002; Giovannetti et al., 2002; Hart et al., 1998). In contrast, as was shown in Chapter 1, the EAT appears to be a valid proxy of error awareness on real world tasks. It will nonetheless be important for future work to determine the extent to which these findings generalise to other paradigms. Also, while the speeded error signalling response was crucial for assessing error awareness within the context of the accumulation-to-bound account of error awareness, it would be of interest for future work to determine how older adults error awareness is captured by confidence rating scales (e.g. Hewig et al., 2011; Scheffers & Coles, 2000; Shalgi & Deouell, 2012) which permit a finer characterisation of the graded nature of error awareness.

It would also be remiss not to point out that the implication of the right dlPFC in error awareness has not been supported by fMRI studies (Debener et al., 2005; Hester et al., 2005; Hester et al., 2012; Klein et al., 2007; Orr & Hester, 2012). While earlier fMRI studies also failed to find an effect of awareness on pMFC activity it has been suggested that this may have been due to insufficient statistical power as two recent studies with particularly large sample sizes found that pMFC activity was indeed significantly greater for errors that were followed by awareness compared to those that were not (Hester et al., 2012; Orr & Hester, 2012). However, even these studies with large sample sizes did not highlight the right dlPFC as being sensitive to awareness. The possibility that the involvement of the right dlPFC, as documented in this thesis, is a consequence of the general increase in frontal lobe recruitment that is known to occur with increasing age (Chapter 1) should certainly be verified by future studies. However, this explanation is not easily reconciled with the compelling evidence of a strong association between the capacity for awareness and right dlPFC across several different clinical populations. As suggested in Chapter 5, another plausible explanation for this discrepancy is that all fMRI studies of error awareness to date have employed event-related designs, whereby the focus is on the brain activations in response to the error itself. The proposed proactive and sustained role of the right dlPFC in error awareness would not be captured using this approach. Future fMRI studies of error awareness should therefore aim to employ mixed blocked/event-related designs, which facilitate the characterisation of sustained task-set processes (Donaldson, 2004; Dosenback et al., 2006).

Many of the inferences drawn throughout this thesis were based either directly or indirectly on the conceptualisation of error awareness as a decision process, but much work is still required to verify aspects of this account. For instance, as pointed out in chapters 1 and 3, much of what is known about decision-making processes has been derived from perceptual discrimination tasks. One fundamental difference between perceptual decision

making and error awareness is that in accounts of the former decisions are solely determined by first-order sensory evidence accumulation derived from stimuli during task performance, whereas the latter likely involves the accumulation of second-order evidence from multiple sources (e.g. peri-error response conflict, interoception of autonomic responses accompanying the error, proprioceptive feedback, continued post-error sensory processing; Ullsperger et al., 2010). It is possible to manipulate sensory evidence relatively easily to observe downstream effects on components of the perceptual decision process (e.g. O'Connell et al., 2012). In contrast, explicating the factors that contribute to the error awareness decision process is constrained by the difficulty inherent in isolating the neural substrates for each of the many putative sources of second-order evidence. It also remains largely unclear how the strength of second-order decision evidence can be manipulated experimentally. Previous research, as well as the work within this thesis, has supported the idea that error-evoked pMFC activity provides one source of second-order error evidence that is accumulated by the Pe. However, future research should endeavour to isolate and verify other neural substrates of second-order evidence that feed into the error awareness decision process, and also aim to determine the extent to which these other sources of evidence are implicated in older adults error awareness deficits.

Another issue pertaining to the conceptualisation of error awareness as a decision process concerns the lack of clarity about *how* multiple sources of evidence might be combined to form the compound error signal represented by the Pe component. Research from perceptual decision making hints at possible directions for future research in this regard. For instance, a number of lines of evidence have suggested oscillations may play a key role in the accumulation of sensory evidence during perceptual decision-making. For instance, recent research using magnetoencephalography (MEG) has indicated that visual cortex activity in the gamma-band (60-100 Hz) encodes the strength of evidence during the presentation of stimuli (Siegel et al., 2007), and decision-predictive activity over M1 in the same EEG frequency band reflects the temporal integral of this sensory evidence signal (Donner, Siegal, Fries, & Engel, 2009). This work suggests that at least in the context of perceptual decision-making, gamma oscillations facilitate both the initial encoding of this evidence as well as the communication between different cortical areas while this evidence is being encoded. An earlier analysis of the same MEG data reported in the 2009 paper by Donner et al. additionally revealed an interaction between posterior parietal cortex and LPFC in the lower beta frequency band (12-25 Hz) present from the offset of the stimulus up until before decision report, which was predictive of the accuracy of the upcoming decision (Donner, Siegel, Oonstenveld et al., 2007). It has been suggested that these functional interactions facilitated by beta oscillations may reflect communication between these brain

regions as they actively maintain a representation of the sensory evidence. As already mentioned such continued processing of sensory information may be one possible determinant of error awareness (Steinhauser et al., 2008; Ullsperger et al., 2010). Further, in performance monitoring research theta oscillations have been implicated as the primary mechanism by which pMFC interacts with other brain regions to communicate the need for the regulation of cognitive control (Cavanagh et al., 2009; Cohen & van Gaal, 2012), and a fundamental assumption of this thesis is that MF theta represents an important source of error evidence (Murphy et al., 2012). It is thus apparent that decision-making and performance monitoring are characterised by the transfer of multiple kinds of information between brain regions via oscillatory dynamics at various frequency bands. Accordingly, there may be basis, albeit tentative, for hypothesising that oscillatory activity at different frequencies between different brain regions may correspond to discrete forms of second-order decision evidence and that these signals are consolidated in the compound error signal that ultimately informs the error awareness decision. The manner in which this form of integration might be achieved is far from clear, however, and much work will be required in order to validate this hypothesis.

7.2 The potential of tDCS as a tool for ameliorating error awareness

7.2.1 Contributions

While identifying and elucidating the nature of age-related deficits is of great importance, there is tantamount onus on the field of cognitive neuroscience to make use of this information to devise and validate approaches to remediate these deficits, and if possible, prevent them from occurring in the first place. Concurrent to establishing whether the right dlPFC had a causal role in supporting error awareness in older adults, another primary objective of the empirical work within was chapters 5 and 6 was to assess the potential for tDCS to be used as a tool for remediating error awareness deficits.

As mentioned in Chapter 4 in addition to its value as a scientific tool, tDCS has been identified as a non-invasive approach for producing prolonged clinically significant improvements in a number of psychiatric and neurological conditions such as depression (Kuo et al., 2014; Brunoni et al., 2013), stroke (Floel, 2014), and chronic pain (Jensen et al., 2014). The potential for tDCS to ameliorate deficits resulting from cognitive ageing has only

begun to be explored recently, but a number of studies have documented tDCS induced improvements in domains such as working memory (Berryhill & Jones, 2012; Seo et al., 2011), decision-making (Paulo et al., 2010), object location learning (Flöel et al., 2012), skill acquisition (Zimerman & Hummel, 2010), word retrieval (Meinzer et al., 2014; Ross et al., 2011) and word generation (Meinzer et al., 2013) in older adults.

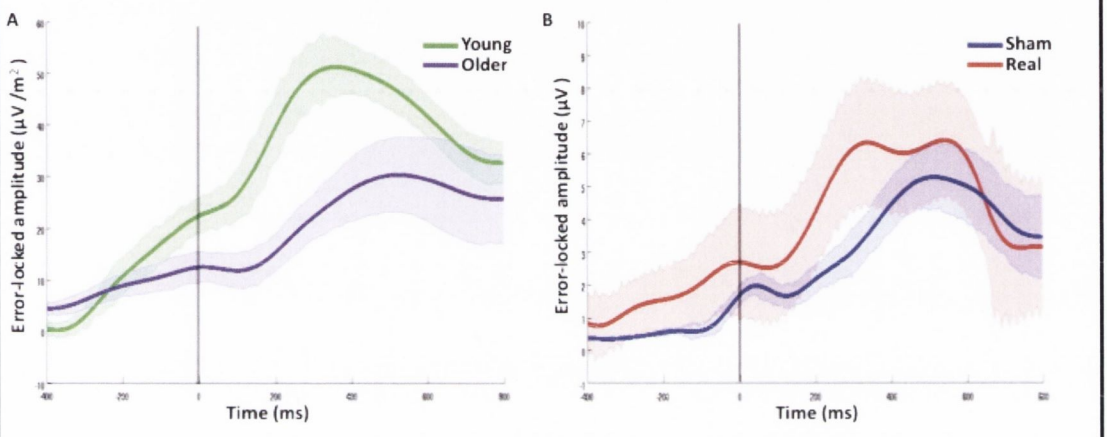

Figure 7.1 The effect of transcranial direct current stimulation on the error positivity of older adults appears to resemble a change towards more youth-like processing. The error-locked error positivity (Pe) waveforms of young and older adults (**A**; Chapter 3) alongside the error-locked Pe waveforms of older adults for Online Real and Sham tDCS (**B;** Chapter 5). Given that these figures were derived from separate samples and separate studies, direct comparisons cannot be made. However, it is interesting to note that the change in build-up rate and peak latency of older adults Pe following Real tDCS, renders it more similar to that of younger adults.

The unit of measurement for amplitude in **A is micro-volts per metre squared as a current source density transformation was applied to the EEG data (see Chapter 3); it was not possible to apply this transformation to the data in **B** due to the uneven distribution of recording sites following the placement of the tDCS electrodes.*

The present thesis provided the first demonstration that tDCS can also produce improvements in older adults' error awareness. Between chapters 5 and 6 a significant improvement in error awareness for Repeat No-go trials was observed during anodal stimulation in three separate experiments. In each demonstration the magnitude of the improvement was consistently between 10 and 13%, and could not be accounted for by changes in accuracy, slower response times, the neuromodulatory influence of the reference electrode, or expectancy effects due to greater somatic sensation. From a clinical perspective it is interesting to note that stimulating the right dlPFC not only brought behavioural performance closer to that observed in young adults in Chapter 3, it also modified their error-

related electrophysiological responses in a manner that was indicative of more youth-like processing (see **Figure 7.1**).

The translational potential of these findings, however, largely depends on the ability of tDCS to produce long-term changes in error awareness. Previous research suggests that to obtain improvements that persist for periods in the order of weeks to months, multiple consecutive sessions of tDCS would be required (Boggio et al., 2012; Doruk et al., 2014; Joen & Han, 2012). While multiple sessions were not administered in the present thesis, in Chapter 6 it was found that improvements in error awareness, as well as the two tightly related electrophysiological signals, MF theta and the Pe, were still evident for at least ~26 minutes following stimulation. Given that post-stimulation effects, irrespective of duration, are understood to involve LTP mechanisms (Chapter 4), this observation provides rationale for being optimistic about the utility of tDCS for inducing enduring plastic changes in the neural substrates that support error awareness.

The benefits of improved error awareness could be manifold, from better recognition of errors in the context of everyday activities such as the management of medication and driving, to facilitating more accurate appraisals of cognitive abilities that would conceivably guide more adaptive behaviour. In addition to this, enhanced error awareness may indirectly confer benefits to other cognitive functions by eliciting intrinsic motivation for implementing compensatory strategies, or fostering willingness to actively engage in activities that have been known to reduce the risk of dementia, such as cognitively demanding tasks and physical activity (Wang et al., 2012).

Furthermore, as argued above, the tDCS-induced improvements in error awareness may be primarily due to enhancing the capacity of the right dlPFC to fulfill its role in sustained attention. The observation that stimulation of the right dlPFC produced improvements in MF theta power that were not unique to error trials in Chapter 6 supports this hypothesis, and additionally hints at the possibility that this tDCS protocol may produce gains in many other performance monitoring and cognitive control processes that have also been associated with theta oscillations in the medial frontal cortex (Cavanagh et al., 2012; Cohen & Cavanagh, 2011; Kahana et al., 2001; Nigbur et al., 2011; Van de Vijver et al., 2014). Indeed, the implication of attentional processes in this manner may point to the potential for the tDCS effects to generalise to even more diverse cognitive domains. This reasoning is based on the understanding that improving core, supportive processes such as attention can have generalised effects by enhancing the overall input to cognitive processing, providing a more stable and effective substrate for other cognitive capacities (Sohlberg & Mateer, 2001). Of particular relevance in the context of the present thesis, the potential for

improved attention to enhance the input to memory systems (Sohlberg & Mateer, 2001) may provide an explanation for the link that was observed between online error awareness and general representations of cognitive abilities in Chapter 2.

7.2.2 Limitations and Future directions

As mentioned above, a priority for future work should be to assess the feasibility of tDCS to produce improvements in error awareness that would last beyond the short-term, and also assess whether, in the long-run, the effects on error awareness correspond to improvements in real world measures of awareness such as discrepancy scores on the Cognitive Failures Questionnaire and Memory Functioning Scale. One factor that currently appears as though it may at least partially limit the translational potential of these findings is the substantial inter-individual variability in responsiveness to the intervention that was observed in all three demonstrations. As discussed in Chapter 4, substantial inter-individual variability is a pervasive finding in the non-invasive brain stimulation literature. There are many reasons why such variability might exist such as individual differences in neurotransmitter efficiencies, genetic polymorphisms, brain structure, brain areas recruited during task performance, level of function within the targeted region, years of education and age. In Chapter 5, two of the possible inter-individual determinants of stimulation effects (Age and Years of Education) were explored but no significant effects were observed. A major challenge inherent in attempts to developing tDCS as a clinical tool for remediating error awareness deficits will thus be to quantify this inter-individual variation and to determine its origins. Generally, the understanding of such factors would hopefully contribute to more informed and efficient application of tDCS, such that it can be utilised to its full potential in both basic and clinical research.

The EAT paradigm warrants discussion again under this section, particularly due to the fact that the tDCS-induced improvements in error awareness were confined to Repeat No-go trials. As pointed out in Chapter 5, this finding may suggest that tDCS has affected a cognitive process that is specific to Repeat No-go trials, such as working memory. However, this explanation is at odds with three observations: 1) accuracy on the primary task did not vary across Real and Sham conditions; 2) the finding that when accuracy is free to vary, rates of error awareness and overall error rates are uncorrelated (O'Connell et al., 2009); and 3) the observation that error awareness on the EAT correlates with awareness of cognitive function in every day life (Chapter 2). Further, although there was no distinction made between trial types in the analyses carried out in Chapter 2, a subsequent re-analysis of the correlations between error awareness on the EAT and the discrepancy scores on the CFQ and

MFS revealed that these relationships were stronger for Repeat No-go trials (r = -.408, p < .017; r = -.327, p < .017, respectively) compared to Stroop No-go trials (r = -.169, p > .017; r = -.356, p < .017, respectively). It has been argued that a more plausible explanation for the absence of the effect on Stroop No-go trials may be that performance was close to ceiling in all demonstrations, likely leaving little room for further improvements. This hypothesis is consistent with studies that have found that tDCS-induced facilitatory effects were more pronounced when levels of impairment were more severe (Hummel et al. 2006), and that improvements were not evident when baseline levels of performance were already high (Kang et al. 2009; Tseng et al., 2012). Nevertheless, as mentioned above, it will be important for future work to determine the extent to which these findings generalise to other paradigms. Finally, it will also be important to explicitly test the hypothesis that the tDCS-induced improvements in error awareness are mediated by improvements in sustained attention. A first step in this direction may be to investigate the effect of the exact same tDCS protocol over right dlPFC on participants performance of a sustained attention task such as the sustained attention to response task (SART; Robertson et al., 1997).

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