

Electrocortical Indices of Cognitive Control in Working Memory:
Exploring the Effects of Proactive Interference, Cognitive Load, and Aging

by

William James Tays

A thesis
presented in partial fulfillment
of the requirements for the degree
of Doctor of Philosophy

Faculty of Social Sciences
Brock University
St. Catharines, Ontario

© 2011

General Abstract

Cognitive control involves the ability to flexibly adjust cognitive processing in order to resist interference and promote goal-directed behaviour. Although frontal cortex is considered to be broadly involved in cognitive control, the mechanisms by which frontal brain areas implement control functions are unclear. Furthermore, aging is associated with reductions in the ability to implement control functions and questions remain as to whether unique cortical responses serve a compensatory role in maintaining maximal performance in later years. Described here are three studies in which electrophysiological data were recorded while participants performed modified versions of the standard Sternberg task. The goal was to determine how top-down control is implemented in younger adults and altered in aging. In study 1, the effects of frequent stimulus repetition on the interference-related N450 were investigated in a Sternberg task with a small stimulus set (requiring extensive stimulus resampling) and a task with a large stimulus set (requiring no stimulus resampling). The data indicated that constant stimulus resampling required by employing small stimulus sets can undercut the effect of proactive interference on the N450. In study 2, younger and older adults were tested in a standard version of the Sternberg task to determine whether the unique frontal positivity, previously shown to predict memory impairment in older adults during a proactive interference task, would be associated with the improved performance when memory recognition could be aided by unambiguous stimulus familiarity. Here, results indicated that the frontal positivity was associated with poorer memory performance, replicating the effect observed in a more cognitively demanding task, and showing that stimulus familiarity does not mediate compensatory cortical activations in older adults.

Although the frontal positivity could be interpreted to reflect maladaptive cortical activation, it may also reflect attempts at compensation that fail to fully ameliorate age-related decline. Furthermore, the frontal positivity may be the result of older adults' reliance on late occurring, controlled processing in contrast to younger adults' ability to identify stimuli at very early stages of processing. In the final study, working memory load was manipulated in the proactive interference Sternberg task in order to investigate whether the N450 reflects simple interference detection, with little need for cognitive resources, or an active conflict resolution mechanism that requires executive resources to implement. Independent component analysis was used to isolate the effect of interference revealing that the canonical N450 was based on two dissociable cognitive control mechanisms: a left frontal negativity that reflects active interference resolution, but requires executive resources to implement, and a right frontal negativity that reflects global response inhibition that can be relied on when executive resources are minimal but at the cost of a slowed response. Collectively, these studies advance understanding of the factors that influence younger and older adults' ability to satisfy goal-directed behavioural requirements in the face of interference and the effects of age-related cognitive decline.

Acknowledgements

Through all the high points and low points I've had to traverse in the journey to complete this thesis, I have had the support of a tremendous group of colleagues and friends. Without them, the work I report herein would not be of as high a calibre or have been such a pleasure to complete.

First, I must thank my advisor, Jane Dywan, for her subtle but firm guidance over the past several years. I'm a better researcher and better writer due to her support. I thank Sid Segalowitz for making available his superlative ERP expertise and for his attention to the greater context that all our focused research projects inhabit. I am ever-appreciative to Karen Arnell, for always having a fresh and insightful perspective on my work.

I'd like to thank everyone in the Brock University Cognitive and Affective Neuroscience Lab for their help in making my projects a success. In particular I am indebted to James Desjardin for his technical and programming assistance. I am grateful to Lesley Capuana for helping me collect the data for my aging study. I am also thankful to Tim Murphy for always having an open door and time to listen.

Last, I must thank all my friends and family for trusting in my choices and always encouraging my efforts.

With great appreciation,

-W.J. Tays

General Abstract

Cognitive control involves the ability to flexibly adjust cognitive processing in order to resist interference and promote goal-directed behaviour. Although frontal cortex is considered to be broadly involved in cognitive control, the mechanisms by which frontal brain areas implement control functions are unclear. Furthermore, aging is associated with reductions in the ability to implement control functions and questions remain as to whether unique cortical responses serve a compensatory role in maintaining maximal performance in later years. Described here are three studies in which electrophysiological data were recorded while participants performed modified versions of the standard Sternberg task. The goal was to determine how top-down control is implemented in younger adults and altered in aging. In study 1, the effects of frequent stimulus repetition on the interference-related N450 were investigated in a Sternberg task with a small stimulus set (requiring extensive stimulus resampling) and a task with a large stimulus set (requiring no stimulus resampling). The data indicated that constant stimulus resampling required by employing small stimulus sets can undercut the effect of proactive interference on the N450. In study 2, younger and older adults were tested in a standard version of the Sternberg task to determine whether the unique frontal positivity, previously shown to predict memory impairment in older adults during a proactive interference task, would be associated with the improved performance when memory recognition could be aided by unambiguous stimulus familiarity. Here, results indicated that the frontal positivity was associated with poorer memory performance, replicating the effect observed in a more cognitively demanding task, and showing that stimulus familiarity does not mediate compensatory cortical activations in older adults.

Although the frontal positivity could be interpreted to reflect maladaptive cortical activation, it may also reflect attempts at compensation that fail to fully ameliorate age-related decline. Furthermore, the frontal positivity may be the result of older adults' reliance on late occurring, controlled processing in contrast to younger adults' ability to identify stimuli at very early stages of processing. In the final study, working memory load was manipulated in the proactive interference Sternberg task in order to investigate whether the N450 reflects simple interference detection, with little need for cognitive resources, or an active conflict resolution mechanism that requires executive resources to implement. Independent component analysis was used to isolate the effect of interference revealing that the canonical N450 was based on two dissociable cognitive control mechanisms: a left frontal negativity that reflects active interference resolution, but requires executive resources to implement, and a right frontal negativity that reflects global response inhibition that can be relied on when executive resources are minimal but at the cost of a slowed response. Collectively, these studies advance understanding of the factors that influence younger and older adults' ability to satisfy goal-directed behavioural requirements in the face of interference and the effects of age-related cognitive decline.

Acknowledgements

Through all the high points and low points I've had to traverse in the journey to complete this thesis, I have had the support of a tremendous group of colleagues and friends. Without them, the work I report herein would not be of as high a calibre or have been such a pleasure to complete.

First, I must thank my advisor, Jane Dywan, for her subtle but firm guidance over the past several years. I'm a better researcher and better writer due to her support. I thank Sid Segalowitz for making available his superlative ERP expertise and for his attention to the greater context that all our focused research projects inhabit. I am ever-appreciative to Karen Arnell, for always having a fresh and insightful perspective on my work.

I'd like to thank everyone in the Brock University Cognitive and Affective Neuroscience Lab for their help in making my projects a success. In particular I am indebted to James Desjardin for his technical and programming assistance. I am grateful to Lesley Capuana for helping me collect the data for my aging study. I am also thankful to Tim Murphy for always having an open door and time to listen.

Last, I must thank all my friends and family for trusting in my choices and always encouraging my efforts.

With great appreciation,

-W.J. Tays

Table of Contents

	Page
Chapter 1: General Introduction.....	1
Proposed Studies.....	15
Chapter 2: General Proactive Interference and the N450 Response.....	20
Method.....	23
Results.....	27
Discussion.....	29
Chapter 3: Age-Related Differences during Simple Working Memory Decisions: ERP Indices of Early Recognition and Compensation Failure.....	30
Method.....	37
Results.....	40
Discussion.....	46
Chapter 4: Interference Detection or Resolution? Delineating the Time Course and Function of the N450 with Cognitive Load and Independent Component Analysis.....	53
Method.....	62
Results.....	68
Discussion.....	77
Chapter 5: General Discussion.....	85
Future Studies.....	62
Footnotes.....	101
References.....	104
Tables.....	126
Figures.....	135
Appendix A: Notes on Independent Component Analysis.....	157

List of Tables

Table 2.1 Examples of condition manipulations.....	127
Table 2.2 Mean N450 amplitudes for each condition of the large and small set size tasks.....	128
Table 3.1 Mean accuracy and response times.....	129
Table 3.2 Mean amplitudes for key statistical analyses.....	130
Table 4.1 Mean percentage errors.....	131
Table 4.2 Mean response times.....	132
Table 4.3 Mean N450 amplitude from select frontal sites.....	133
Table 4.4 Mean N450 _{ICA} amplitudes from select frontal sites.....	134

List of Figures

Figure 2.1 A schematic diagram of the procedure.....	136
Figure 2.2 Behavioural data for small and large set size tasks.....	137
Figure 2.3 Scalp topographies and waveforms for the N450 for a) the small set size task and b) the large set size task.....	138
Figure 3.1 Experimental procedure for the Sternberg task and the incidental memory task.....	140
Figure 3.2 Stimulus-locked grand-average waveforms for a) the Sternberg task and b) the incidental memory.....	141
Figure 3.3 Topographies for the early posterior negativity and frontal positivity for younger and older adults in the Sternberg task.....	143
Figure 3.4 The scatterplot of the linear relation between Sternberg accuracy and mean frontal positivity in older adults.....	144
Figure 3.5 The scatterplot of the linear relation between the early posterior negativity with a) mean Sternberg accuracy and b) mean Sternberg RT.....	145
Figure 4.1 A schematic of the load Sternberg task showing a) the four-item array and b) a graphical representation of the different conditions.....	146
Figure 4.2 The 64 channel montage used in the ICA decomposition.....	147
Figure 4.3 Selected channels showing frontal negativities associated with the N450 at low (a), medium (b), and high (c) working memory load.....	148
Figure 4.4 Selected channels showing frontal negativities associated with the N450 _{ICA} at low (a), medium (b), and high (c) working memory load.....	151

Figure 4.5 Topographies showing the PI effect for each of familiar and response conflict trials at 450 ms after the probe.....154

Figure 4.6 GeoSource models of the neural sources for activation based on grand average difference waves (PI minus negative) from the low and high memory loads.....155

Figure 4.7 BESA model and source waveforms showing right frontal, left frontal and ACC dipole activations for each load.....156

Chapter 1: General Introduction

Working Memory: The Multicomponent Model and Role of the Frontal Lobes

The capacity-limited nature of human cognition makes it vital to selectively process and attend to goal-relevant information. Relevant information no longer available in the environment is actively maintained in working memory as internal representations (Miller, Galanter, & Pribram, 1960). The most prominent cognitive theory to emerge from early investigation of the properties of working memory is the multi-component model developed by Baddeley and Hitch (1974; Baddeley, 1986; 2000; for an extensive review of empirical support of the multi-component model from behavioural paradigms see Repovš & Baddeley, 2006). The importance of the multi-component model, as opposed to previous models specifying a unitary storage function by a more passive short-term memory system (e.g., Atkinson and Shiffrin, 1968), was the emphasis on the functional significance of short-term storage for cognition and behaviour. Also of key importance was the sub-division of such processes into separate verbal and visuospatial domains, and the conceptualization of a central executive that directed the two domain-specific slave systems (Baddeley & Hitch, 1974).

Briefly, in the multi-component model the storage of verbal information depends on a phonological store that serves as a buffer for verbal information, and an articulatory rehearsal system that refreshes or maintains the contents of the buffer. These particular components arose in responses to curious findings from classic digit/word span experiments. For instance, the phonological similarity effect (e.g., Conrad & Hull, 1964) and articulatory suppression effect (e.g., Baddeley, Lewis & Vallar, 1984) were taken as evidence of the phonological nature of representation in working memory, whereas the

word length effect (e.g., Baddely, Thompson, & Buchanan, 1975) was suggestive of covert serial rehearsal similar to vocal articulation itself. Visual and spatial information, on the other hand, were thought to be stored in a visuospatial sketchpad (Baddeley, 2003), and may include discrete storage and rehearsal functions (i.e., the visual cache and inner scribe, respectively; Logie, 1995). Central to the model is the tenet that each of the verbal and visuospatial buffers in working memory are distinct but both controlled by the same limited-capacity central executive that guided and implemented the functions of the slave systems (Baddeley, 1974). This central executive was intentionally portrayed in vague terms as a homunculus that performed all acts involving controlled attention, decision making, and information integration functions because such processes were poorly understood at the inception of the model (Baddeley, 2001).

As a final point, the original tripartite system has seen an addition of a new subsystem, the episodic buffer (Baddeley, 2000; Baddely, 2001), to account for data inconsistent with the original model such as the binding of verbal and visual code (Chincotta et al., 1999), and the bridging of long-term memory and the slave systems (Baddeley & Andrade, 2000). The episodic buffer is assumed to operate on a multi-modal code whereby verbal, visuospatial, and long-term memory may interact (dependent on the application of executive attention) in order to create a more complete representation of the environment with which to manipulate information, solve problems, and act upon conscious goals (Baddeley, 2000; Baddely, 2001).

Whereas neuropsychology research makes a relatively clear case for frontal cortices supporting the central executive of the multi-component working memory model (Miller & Cohen 2001; but see also Alvarez & Emory, 2006), there is clear and

consistent evidence from human neuropsychology in opposition to suggestions that frontal areas also support general mnemonic buffer functions (D'Esposito, Cooney, Gazzaley, Gibbs & Postle, 2006; Della Sala, Gray, Spinnler & Trivelli, 1998; D'Esposito et al, 1999; Müller et al., 2006). As a classic example, Donald Hebb's early writings on intelligence and the brain describe a woman who had survived extensive, though incomplete, resection of bilateral frontal cortex to remove a primary glioblastic tumour. Although the subject exhibited typical symptoms of what would later be called 'dysexecutive syndrome' (Baddeley, 1996), her simple digit-span capacity was left intact (Hebb, 1939). Other studies on the impact of frontal lobe lesion on simple verbal, digit, and spatial span mirror this result (see D'Esposito et al., 2006; Della Sala et al. 1998; Postle et al. 1999).

Other research has identified impairments in delayed-response tasks following frontal lobe lesions but only under testing conditions that place additional requirements on executive functions. For instance, impairments can be seen if delay-to-match targets are subsequently repeated later in the testing stream, although no impairment is seen when targets are always unique (Milner, Petrides & Smith, 1985). Therefore, it could be that deficits in short-term storage appear only when a failure to integrate temporal information leads to interference from repetition of salient stimuli (Müller et al., 2006). This explanation is consistent with the observation that frontal lobe patients show difficulty in discriminating target and irrelevant stimuli in auditory (Knight, Scabini & Woods, 1989), somatosensory (Knight, Staines, Swick & Chao, 1999) and visual (Barceló, Suwazono, & Knight, 2000) domains, as well as difficulty inhibiting prepotent response tendencies (Drewe, 1975; Perret, 1974).

Cognitive Control in Working Memory

Cognitive control, often considered synonymous with the executive functions attributed to Baddeley's central executive (Baddeley, 1992), refers to information processing functions that monitor and adjust more low-level processes. Thus, they are thought to support the deployment of attention, the maintenance and manipulation of internal representations, the maintenance and updating task demands, and the selection and execution of behavioural responses (see Hommel, Ridderinkhof, & Theeuwes, 2002). Miller and Cohen (2001) suggest that these higher order control functions are subserved by multiple dissociable sub-processes that may operate under different task demands. Neuropsychological data support the existence of multiple cognitive control processes because of the low interrelation between participants' performance on different neuropsychological tests that are purported to require cognitive control (Burgess & Shallice, 1997; Shilling, Chetwynd, & Rabbitt, 2002) and the poor performance of single dimension models in factor analysis (Miyake, Friedman, Rettinger, Shah, & Hegarty, 2001).

Like the central executive, cognitive control is broadly assumed to be dependent on processes within the frontal lobes (e.g., Miller 2000) and, although the precise functional role (i.e., the when, how, and why) of frontal involvement in cognitively demanding tasks is far from clear (Miller & D'Esposito, 2005), continuing research has generally validated the classic model of anterior brain areas supporting cognitive control in a top-down manner (Badre & Wagner, 2005; Banich, et al., 2000; Crottaz-Herbette & Menon, 2006; Derrfuss, Brass, Neumann, & von Cramon, 2005; Egner, Etkin, Gale, & Hirsch, 2008; Fan, Hof, Guise, Fossella, & Posner, 2008; Fuster, 2000; Kerns, Cohen,

MacDonald, et al., 2004; Milham, Banich, & Barad, 2003; Ridderinkhof, Nieuwenhuis, & Braver, 2007; Rushworth, Walton, Kennerley, & Bannerman, 2004).

As an example, Bunge, Ochsner, Desmond, Glover and Gabrieli (2001) used fMRI to investigate the neural contributors supporting the maintenance of working memory load and interference resolution in prefrontal cortex (PFC). Participants were required to keep either 1, 4 or 6 letters in mind over a short delay and then indicate whether a presented probe matched (positive probe) or did not match (negative probe) any letter in the target set. An interference manipulation was also done as a subset of the 4-letter condition, such that the current negative probe had been presented as a member of the target set on the just previous trial. This design was intended to reveal brain areas recruited for supporting increased working memory load and, separately, brain areas involved in interference resolution. A variety of brain areas were activated during all conditions including bilateral dorsolateral and ventrolateral prefrontal, anterior cingulate, and parietal cortex. However, there were specific neural activations that correlated with interference resolution (left inferior frontal gyrus and right middle frontal gyrus) and load maintenance (anterior cingulate cortex). These results suggested that there were no brain structures uniquely active only during interference resolution, but rather, integrated neural systems provide added support for working memory during conditions of interference or increased load (Bunge et al., 2001).

These findings were in contrast to previous research that suggested a specific role for dorsolateral PFC and parietal cortex in the support of interference resolution (Quintana & Fuster, 1999). However, Quintana and Fuster's (1999) study involved interference resolution specific to response selection rather than just maintaining the

contents of working memory. This suggests that there may be separate systems that subserve conflict resolution in working memory versus conflict resolution in response selection. There is also evidence for a functional dissociation between these two processes. Filtering the contents of working memory is closely associated with ventrolateral PFC (Hazeltine, Poldrack & Gabrieli, 2000; Konishi, Nakajima, Uchida, Kikyo, Kameyama et al., 1999; Thompson-Schill, D'Esposito, Aguirre & Farah, 1997) whereas the selection of task-relevant responses is associated with dorsolateral PFC (Narayanan, Prabhakaran, Bunge, Christoff, Fine et al, 2005; D'Esposito, Postle, Ballard & Lease, 1999; Cohen and Servan-Schreiber, 1992).

Cognitive Control Across the Lifespan

The neural networks supporting cognitive control develop throughout childhood (e.g., Fair et al., 2007) and can be associated with neurodevelopmental milestones in frontal cortex (Fuster 2002; Segalowitz & Davies, 2004) as reflected in the increasing complexity and efficiency of cognitive operations carried out by children of increasing age. Moreover, after maturation-related changes in brain structure and function are completed, by approximately the third decade of life, there are detectable declines in cognitive function (see Salthouse 2009, for a focused discussion of these issues in longitudinal and cross-sectional research). The view that subtle cognitive decline can begin well before old age (often considered for simplicity to begin around age 60) is generally consistent with neuropsychological research that shows detectable reductions in brain volume (e.g., Allen, Bruss, Brown, & Damasio, 2005; Fotenos, Snyder, Girton, Morris, & Buckner, 2005), cortical thickness, (e.g., Salat et al., 2004), the integrity of cortical myelin (e.g., Sullivan & Pfefferbaum, 2006), and alterations in levels of

neurotransmitters such as dopamine (e.g., Erixon-Lindroth et al., 2005) in otherwise healthy individuals. Although information processing efficiency continues to decline through the 60's, 70's and 80's, it must also be stated that there is considerable variance in levels of decline depending on the type of task or function that is investigated (Park 2000). Additionally, large individual differences can be observed across older adults independent of age (e.g., Rapp & Amaral, 1992; Volkow et al., 2000) with some individuals maintaining very high levels of cognitive performance well into their later years.

Sources of variance notwithstanding, the last three decades of research on cognitive aging have seen great advances in knowledge on the various natural changes that occur in information processing in healthy older adults. Aging is associated with changes to high level/top-down cognitive functions, such as episodic memory (Nyberg, Backman, Erngrund, Olofsson, & Nilsson, 1996), stimulus encoding (Cabeza et al., 1997), working memory (Reuter-Lorenz et al., 2000; Morris, Gick, & Craik, 1988; Rypma & D'Esposito, 2000), and executive/attentional control (Buckner 2004; Dywan, Segalowitz, & Arsenault, 2002; Kok 2000; Salthouse, Atkinson, & Berish, 2003; Verhaeghen & Cerella, 2002). While specific posterior brain areas are also affected during aging (Greenwood 2000), the effect of structural and functional changes in these frontal brain regions may be strongest when they are engaged in the higher-order functions mentioned above (e.g., Peiffer et al., 2009).

Theoretical accounts of these cognitive changes include both global factors and specific processing deficits, the prior exemplified by theories of reduced processing speed (e.g., Salthouse, 1996), and the later by the inhibitory control deficit theory of

aging (e.g., Hasher & Zacks, 1988; Hasher, Quig, & May, 1997). Initially, Salthouse (1988) proposed that the difficulties older adults experience from distraction results from a reduction in their speed of processing and, therefore, alterations in the temporal order in which specific elements of information processing are completed. For example, the decision process involved in identifying a visual stimulus as "irrelevant" may take longer in older adults compared to younger adults. If this delay were sufficiently long, sensory information may begin to degrade and could force further processing to react to the stimulus-based traces in working memory. This slowing was initially attributed to a reduction in general cognitive resources or "cognitive fuel" (Hartley, 1992). In cognitively demanding tasks, such as the Stroop task, controlling for speed of processing partially attenuated the performance differences between older and younger adults (Salthouse & Meinz, 1995).

Hasher, Zacks and May (1999) subsequently argued that efficient information processing depends upon controlled attention and the management of working memory, such that goal-relevant stimuli are processed and non-relevant stimulus processing is restrained or suppressed. The mechanisms thought to accomplish this involved controlling access to working memory and the deletion of irrelevant items in working memory (Hasher et al, 1999). A failure to control access or to delete no-longer-relevant items would allow irrelevant stimuli to enter or remain in working memory. The immediate consequence of this invasion into working memory is that, because of its limited capacity, the efficient representation and manipulation of relevant information would become more difficult. In addition, occupying working memory allows irrelevant representations to receive sustained activation, and hence be encoded into long term

memory (Hasher et al., 1999; 1988). As a result, behaviourally relevant information is not encoded as efficiently as it normally would be, setting the stage for difficulties in accessing required information at a later time. This is particularly important during discourse comprehension in which an individual must rely on the "timely retrieval of information necessary to establish coherence among certain critical ideas" (Hasher and Zacks, 1988). Essentially, older adults with difficulties inhibiting the entrance of distracting information into working memory will have difficulties retrieving and acting upon behaviourally relevant information at a later time.

These fundamental frameworks for viewing cognitive aging have been complemented by evidence from cognitive neuroscience research that employs structural, i.e. MRI and diffusion tensor imaging (DTI), as well as functional methods, i.e. fMRI, PET, MEG and EEG, in identifying mechanisms for observed age-related decline. Global processing-speed deficits are supported by evidence of reduced coherence between distant cortical networks (e.g., Andrews-Hanna et al., 2007) and degradation of white matter tracts (e.g., Salat et al., 2005) in older adults. Declines in the executive control tasks, tapping inhibitory control processes for instance, may be explained by the frontal lobe hypothesis of aging wherein the anterior cortical areas that support executive functions are seen as the most sensitive to the effects of aging (Raz 1999; West 1996; but see also Greenwood 2000).

Whereas there is little doubt that these theoretical frameworks have considerable power in predicting the behavioural outcomes of aging, the structural and neurophysiological changes instigating alterations in information processing remain unclear. This is particularly the case for the frontal lobe hypothesis of aging, wherein the

existence of modest quantitative age-related structural and functional change is clear but the nature and extent of the resulting deficit is not straightforward (Band, Ridderinkhof, & Segalowitz, 2002). Furthermore, there is evidence of considerable individual differences in the effects of aging on frontal lobe function mediated by mental training (Ball et al., 2002), physical exercise (Kramer, Erickson, & Colcombe, 2006), cardiovascular health (Raz, Rodrigue, Kennedy, & Acker, 2007), and by functional reorganization of brain processes (Reuter-Lorenz & Lustig, 2005).

Proactive Interference in Working Memory

Working memory may be particularly sensitive to disruptions in cognitive control. Several lines of research have supported the view that age-related declines in working memory efficiency are due to older adults' reduced ability to suppress the processing of nonrelevant information (i.e., the inhibitory deficit theory of aging, Kane & Engle, 2002; Kane, Hasher, Stoltzfus, Zacks, & Connelly, 1994; Lustig, May, & Hasher, 2001; McDowd 1997). Others have argued that poor selective maintenance of task context by older adults may underlie deficits in cognitive control (Braver et al., 2001; West 2004), a deficit that would compromise working memory efficiency. Jacoby, Bishara, Hessels, and Toth (2005) proposed that an early reflexive response to previously seen stimuli "captures" the processing resources of older adults, compromising already taxed executive control (see also Jacoby, Kelley, & McElree, 1999).

In recent years, increased emphasis has been placed on establishing the links between these theoretical models and the neural processes that could support working memory function in hopes of providing a fuller understanding of age-related change across the lifespan. Neuroimaging has been used to identify unique activity related to

cognitive control that might account for young adults' ability to overcome proactive interference in working memory. In a positron emission tomography (PET) study by Jonides, Smith, Marshuetz, Koeppe, and Reuter-Lorenz (1998), participants held four letters in working memory over a short delay period and judged whether a new probe letter was a member of the current memory set. Critically, on a subset of trials, a current non-target probe had been a member of the memory set on a previous trial. This manipulation created a source of proactive interference and increased response time and the chance of an erroneous response to the familiar non-target probe).

Brain scans during correct trials revealed an up-regulation of activity in the left inferior frontal cortex (IFC, specifically Broadmann's area 45) during interference trials, relative to non-familiar, negative probes, indicating a cognitive control function associated with this frontal brain area. In a follow-up study, older adults performed the same working memory task but showed larger interference effects than those seen in young adults accompanied by an attenuated left IFC response (Jonides et al., 2000). These results were suggestive of a breakdown in specific cognitive control components of working memory in older adults as a result of decreased IFC contributions to cognitive control functions.

Thompson-Schill and colleagues (2002) provided evidence in support of the causal link between IFC and neurocognitive responses to proactive interference by studying a frontal lobe patient (R.C.) with a focal lesion in an area of the IFC that overlapped with the region of activation identified by Jonides et al. (1998). They compared R.C.'s performance on the proactive interference-eliciting Sternberg task to that of young adults, same-age controls (45–60 years), older controls (54–81 years), and

patients with damage to other areas of the frontal cortex. All frontal lobe patients showed small declines in working memory performance, but R.C. demonstrated a profound interference effect in both RT and error rate when faced with recently presented negative probes, suggesting a necessary role for the IFC in resolving proactive interference in working memory (Thompson-Schill et al., 2002). Also of note, the older controls' response patterns were more similar to those of R.C. than to those of younger controls, further supporting the notion that older adults' susceptibility to interference effects in working memory may be due to reduced functioning of the IFC.

Using functional magnetic resonance imaging (fMRI) and a variant of the above mentioned Sternberg task with young adults, Nelson, Reuter-Lorenz, Sylvester, Jonides, and Smith (2003) replicated the link between the IFC and simple proactive interference due to stimulus familiarity. However, they also contrasted the familiarity manipulation with a response conflict condition whereby a positive (matching) probe from trial $n-1$ was presented as a negative (non-matching) probe on the current trial. They found that this response-related interference manipulation further increased error rates and RT, relative to familiarity-based interference. Of most importance though, response-conflict trials elicited unique activation in the anterior cingulate cortex (ACC). Taken together, results indicated that the IFC was uniquely associated with resolving proactive interference effects resulting from familiarity, whereas the ACC was uniquely associated with resolving additional interference due to response conflict (see Botvinick, Braver, Barch, Carter, & Cohen, 2001; Kerns et al., 2004; but see also Ridderinkhof, Ullsperger, Crone, & Nieuwenhuis, 2004 for an alternative account of ACC function).

In contrast to imaging findings, electrophysiological data indicate that ACC contributions to cognitive control are not limited to response-level conflict. A phasic medial frontal negativity, referred to as the N450, occurs between 400 and 500 ms following interference-inducing stimuli such as incongruent trials in color–word Stroop tasks (Rebai, Bernard, & Lannou, 1997; West & Alain, 1999). Imaging studies have shown that medial frontal and fronto-lateral areas are activated during incongruent relative to congruent Stroop trials (Derrfuss, Brass, Neumann, & von Cramon, 2005; Kerns et al., 2004) and source analysis of the Stroop-elicited N450 has revealed general agreement, showing a prominent role for the ACC (e.g., Badzakova-Trajkov, Barnett, Waldie, & Kirk, 2009; Liotti, Woldorff, Perez, & Mayberg, 2000), but with additional generators found in left prefrontal (Markela-Lerenc et al., 2004) and anterior prefrontal regions (West, Bowry, & McConville, 2004). Of central concern to the current discussion, the Stroop-induced N450 has been shown to occur on trials involving interference from both response and nonresponse conflict (West et al., 2004), which is counter to Nelson et al.'s (2003) suggestion that conflict-related ACC activations are limited to interference resolution at the response level.

With respect to aging, West and Schwarb (2006) and West (2004) have shown that the N450 generated by older adults is attenuated during the Stroop tasks using either digit-counting and color–word variants, respectively, consistent with results from imaging studies (e.g., Milham et al., 2002). Whereas older adults tended to show reduced amplitudes across ERPs reflecting conflict processing (e.g., N450) or the maintenance of context information (e.g., P300), it is worth noting from West (2004) that older adults produced a frontally-shifted positivity in the late period of the sustained

potential (SP) that was larger than that observed in younger adults. This observation is in line with imaging data indicating unique cortical activations in older adults, possibly due to either compensatory activity (e.g., Cabeza, Anderson, Locantore, & McIntosh, 2002), dedifferentiation of firing (e.g., Logan, Sanders, Snyder, Morris, & Buckner, 2002), or failures of attentional control (e.g., Milham et al., 2002). Separately, West and Schwarb's (2006) findings are also of note because nonresponse conflict trials were contrasted with response conflict trials in both younger and older adults who were divided by their level of frontal lobe functioning (as psychometrically defined). As expected from the frontal lobe hypothesis of aging, low frontal functioning older adults showed the greatest behavioural interference costs while high frontal functioning older adults did not differ systematically from younger adults. This result also emphasizes the importance of considering individual differences within the older population.

Aging and Interference Effects on ERPs in the Sternberg Task: MA Thesis Research

In the line of research discussed above, there were several unresolved issues that I investigated in my Master's research project involving the study of cognitive control functions in younger and older adults using electrophysiological recordings (Tays, Dywan, Mathewson, & Segalowitz, 2008). High-density EEG was recorded while participants completed a modified Sternberg task adapted from Nelson and colleagues (2003). Considering that interference effects can be highly variable with respect to the conditions under which they arise and the resulting brain activation and behavioural outcomes (see Wager et al., 2005), it was not clear whether the N450 effects reported for the Stroop task (e.g., West 2004; West & Schwarb, 2006) would also be observed in the Sternberg task. If we did observe an N450 effect, we wondered whether it would be

reduced in older adults and whether the pattern of neural decline would be consistent with the neuroimaging results reported for the Sternberg task (Jonides et al., 2000). Second, the superior temporal resolution of electrophysiological techniques allowed for the determination of whether the early discrimination and later evaluation of target versus nontarget stimuli (Dywan, Segalowitz, & Arsenault, 2002; Jacoby, Bishara, Hessels, & Toth, 2005) would, indeed, reflect distinct aspects of age-related change in cortical response. Also, using the localization information reported by Nelson et al. (2003), it was possible to conduct a source analysis of event-related potential (ERP) responses, which allowed for testing the timing of specific IFC and ACC activations in response to interference.

Results revealed that both younger and older adults were sensitive to familiarity-based and response-related proactive interference manipulations, although the older adults showed only modestly greater interference cost compared to younger adults. Electrophysiological data revealed that younger adults produced frontal negativities between 400 and 500 ms after interference eliciting Sternberg probes that was similar, though having a more frontal topography, to that seen in variants of the Stroop task (e.g., Markela-Lerenc et al., 2004; West, Bowry, & McConville, 2004). Moreover, young adults showed a modest relationship between the amplitude of a P3a to probe items and the frontal N450 such that greater sensitivity to targets (P3a response) predicted a smaller ERP interference effect (N450). This suggested that, through early attentional selectivity, targets were efficiently discriminated from nontarget stimuli, reducing the need to engage later cognitive control processes. That is, early selection

made later correction less necessary in younger adults (Jacoby, Kelley, & McElree, 1999).

In contrast, older adults did not produce a differentiated P3a response to targets and, in place of the N450, produced a large late positivity (referred to here as the frontal positivity) that was insensitive to conflict manipulations. Thus, it appeared that the mechanisms supporting early target selection and later interference resolution are both altered in older adults. For younger adults, our source models produced the best fit when both ACC and IFC activation were allowed to explain the N450. This was inconsistent with the suggestion by Nelson et al. (2003) that ACC activation is specific to response conflict trials. Because the N450 was identified as the time point of major ACC activation, and because the source model was initially seeded using spatial coordinates from Nelson et al., our study should have provided a powerful test of the role of the ACC in response to different sources of interference.

Although the observed coactivation of the IFC and the ACC did not correspond to the imaging findings of Nelson et al. (2003), they were generally consistent with other ERP studies comparing response-based and non-response-based interference (Badzakova-Trajkov, Barnett, Waldie, & Kirk, 2009; Hanslmayr et al., 2008; Markela-Lerenc et al., 2004; West 2004). These results were also supported by a growing body of evidence (e.g., Bartholow et al., 2005; Ridderinkhof, Ullsperger, Crone, & Nieuwenhuis, 2004) that the ACC works in conjunction with other brain areas to regulate context dependent behaviours (Devinsky, Morrell, & Vogt, 1995), and that it plays a role beyond the detection of perceptually driven response conflict, as often proposed (e.g., Botvinick, Braver, Barch, Carter, & Cohen, 2001; Milham et al., 2001).

As well, the fact that patients with damage to the ACC can resist interference effects and make appropriate adjustments to performance (Fellows & Farah, 2005; Stemmer, Segalowitz, Witzke, & Schönle, 2004) suggests that other frontal brain regions may play a role in conflict monitoring and error detection.

The N450 was also associated with IFC activity in both the left and right hemispheres, consistent with other literature related to the cognitive control functions of these cortical regions (Aron, Robbins, & Poldrack, 2004; Brass, Ullsperger, Knoesche, von Cramon, & Phillips, 2005). Moreover, its role in supporting cognitive control was expected, given its association with interference resolution in a variety of tasks (Cardillo, Aydelott, Matthews, & Devlin, 2004; Derrfuss, Brass, & von Cramon, 2004). Some researchers further specify that, in the context of task-switching and n-back tasks, the IFC may play a role in biasing posterior brain systems to support stimulus–response mappings, thus reinforcing task rules and context requirements (Brass et al., 2005; Derrfuss, Brass, Neumann, & von Cramon, 2005; Derrfuss et al., 2004). This may occur through the enhancement of relevant representations (e.g., Egner & Hirsch, 2005) or through a combination of facilitory and inhibitory processes (e.g., Cardillo et al., 2004).

In young adults, interference-related activity in the ACC and the IFC was predicted by early target processing in the frontal P3a, a component linked to the reorientation of attention to task-relevant stimuli (Kok 2001). This finding fit well with research showing that inputs from frontal cortices may be required when selecting between competing representations in modality-specific sensory areas (Crottaz-Herbette & Menon, 2006). We found that the P3a targetness effect was attenuated (and delayed) in older adults and that it did not predict later interference-related brain responses. West

(2004) also reported delayed P3 responses in older adults and suggested that this reflected inefficiency in activating or updating of task context and may be partly driven by an age-associated disruption of prefrontal dopamine systems (Erixon-Lindroth et al., 2005; Volkow et al., 2000).

Nonetheless, the groups produced similar patterns of differentiation between positive and neutral probes in their P3b response, with greater amplitudes associated with positive probes. In this task context, the P3b was considered to reflect the ongoing application of attentional resources involved in recognizing previously seen items (Dywan et al., 2002; Polich 2007). This allocation of attention may allow for controlled evaluation of salient/familiar stimuli and automatic activation of prepotent stimulus–response mappings (Dywan et al., 2002; Nieuwenhuis, Aston-Jones, & Cohen, 2005) 2002). Together, the P3a and P3b findings suggest that inefficient attentional control in older adults may be particularly important at the early stages of stimulus processing. However, later occurring cognitive control processes can perform an evaluative function (Jacoby et al., 2005), thus maintaining performance if at the cost of protracted response selection and, therefore, increased response latencies. With respect to interference conditions, older adults' ERP responses were not just attenuated in comparison to younger adults, but revealed a unique pattern of activation—a common finding in the aging literature (Cabeza et al., 2004; Park et al., 2004; Reuter-Lorenz 2002).

Some researchers suggest that enhanced bilateral frontal activation can play a compensatory role in buffering older adults from the full impact of age-related neural decline (Cabeza, Anderson, Locantore, & McIntosh, 2002; Grady et al., 1994; Madden et al., 1997; Rosen et al., 2002). Gutchess and colleagues (2005) found that older adults,

relative to younger adults, showed unique activation in the medial frontal cortex during the encoding of complex scenes that were subsequently successfully remembered. The authors suggested that this supplementary frontal activation compensated for inefficient activation in the medial-temporal cortex in the older group. In contrast, other research suggests that unique cortical activity in older adults can be a sign of declining efficiency of information processing (e.g., Logan, Sanders, Snyder, Morris, & Buckner, 2002; Nielson, Langenecker, & Garavan, 2002). As an example, Colcombe, Kramer, Erickson, and Scalf (2005) took fMRI recordings during a perceptual flanker task. They found that greater left frontal activity in older adults (additive to typical right frontal activity in younger adults) was indicative of poor behavioural performance, suggesting that this additional activity is not always compensatory.

In Tays et al. (2008), analysis of individual differences in brain response and behavioural performance in the older adults indicated that unique frontal positivities related to poorer behavioural performance in our interference task. Although the cortical generators of these frontal positivities were not submitted to source analyses, due to extensive between-subjects variability in topography and lack of a prior knowledge of areas that should be seeded with dipoles, ERP findings were consistent with the observations of Reuter-Lorenz et al. (2000) who, through imaging data, observed the typical pattern of bilateral frontal activation in older adults and suggested that this activation could serve a compensatory function. The key difference, however, between this and Tays et al. (2008) was the inclusion of interference trials. It is possible that this engagement of cognitive control processes is responsible for the divergent outcomes. Indeed, the study by Colcombe et al. (2005), as well as the go/no-go task used in

Nielson et al. (2002), shows that additional frontal recruitment was related to poorer behavioural performance in tasks that required the countermanding of prepotent response tendencies. It would appear that older adults were less able to discriminate target from nontarget stimuli as early as younger adults and so were less able to abort processing of salient nontarget probes. In this case, extra activation for processing that information would not be beneficial.

Effects of Aging and Proactive Interference on Working Memory: Doctoral Projects

As is generally the case in scientific research, the findings of Tays et al. (2008) gave rise to many new questions. This doctoral thesis was intended to advance my program of research by further investigating cognitive control functions in younger adults and the individual differences in the cognitive functioning of healthy older adults in the context of various working memory tasks.

Study 1 (Chapter 2). The first question I chose to deal with related to a methodological issue, namely, whether general stimulus repetition in the Sternberg task that was separate from that required by specific proactive interference manipulations could influence the N450 effect. Because the original test set from Tays et al. (2008) consisted of only twenty letters, there was extensive non-specific repetition (items were repeated over 50 times in positions having no relation to task manipulations). The concern was that non-specific stimulus repetition required by small pools of test stimuli may have introduced a weak general interference effect into every trial, including the baseline condition described as having no interference. If true, this would blunt specific interference effects because the 'baseline' condition would not represent a true baseline. It is also possible that general repetition may interact with one or more task conditions,

introducing a confound to task manipulations and compromising the reliability of any conclusions drawn from condition differences.

To preface Chapter 2, this issue was investigated with a very straightforward research design. I adapted the Sternberg task from Tays et al. (2008) to create two tasks using simple three- to five-letter common word stimuli with identical proactive interference manipulations but differing in the pool of stimuli used to create all trials. The task with a small test set was based on twenty short words, similar to what was done using letter stimuli in Tays et al. (2008), and therefore requiring a high degree of general repetition beyond that required by the specific proactive interference manipulations. The second Sternberg task was based on a test set of approximately 500 words, allowing stimulus repetition to be limited to only those stimuli involved in the proactive interference manipulations.

Electrophysiological recordings were taken while healthy young adults completed the two tasks, in counterbalanced order, to determine the effects of general-stimulus repetition effects on behavioural results and on the interference-related N450. It was hypothesized that removing general stimulus repetition would make the N450 interference effect more robust. Conducting this initial study was also important for the subsequent dissertation projects. Isolating the sources of proactive interference in the Sternberg task was necessary before further studying the unique frontal positivity effect in older adults (Chapter 3) and a follow-up investigation of the mechanism(s) underlying the interference-related N450 in younger adults (Chapter 4).

Study 2 (Chapter 3). With regards to older adults, I wanted to continue investigating the nature of the diffuse frontal positive activations observed in older

adults when proactive interference effects are included in the Sternberg task. In my earlier work (Tays et al., 2008), I found that the frontal positivity in older adults was related to poor behavioural performance, providing evidence against compensation as an explanation for this ERP component. However, findings from cognitive aging research, particularly from functional imaging, have shown that up-regulation of cortical activity in the frontal lobes of older adults may be compensatory only under specific task conditions. For instance, if older adults have degraded perceptual processing in posterior sensory cortices then unused reserve capacity in frontal cortex can be brought to bear to boost processing of internal representations (e.g., Reuter-Lorenz 2002). However, when older adults are having difficulty selectively ignoring or aborting the further processing of distracters, then frontal activations indiscriminately bolstering stimulus representation would not be beneficial and, therefore, no longer compensatory (Colcombe et al., 2005). Thus, the issue investigated in Chapter 3 involved probing conditions that could determine whether unique cortical activations in older adults are positively relate to behavioural outcomes.

The Sternberg task from Tays et al. (2008), with its proactive interference manipulations, should benefit minimally from simple up-regulation of processing of all familiar stimuli. This is because a large proportion of the non-target probes are familiar, and, therefore, salient in a similar manner as specific interference-eliciting probes. Thus, to test the nature of the frontal positivities previously observed in older adults, it would be necessary to use a task wherein the up-regulation of processing responses to salient/familiar stimuli is beneficial to task performance. To this end, ERPs were recorded during a simple Sternberg task with no interference manipulations in order to

further investigate these unique frontal activations in older adults. Additionally, to test for the long-lasting effects of possible compensation processes, a simple incidental recognition memory task (for Sternberg probe items) was included. This quick measure gave a second opportunity to see whether differential frontal activation in older adults had a compensatory influence on the long-term retention of information through medial-temporal activation (Daselaar, Fleck, Dobbins, Madden, & Cabeza, 2006). It was hypothesized that the frontal positivity may predict preserved memory performance in older adults, similar to the relationships found in imaging studies using tasks that benefit from non-discriminant up-regulation of familiarity signals during memory judgments.

Study 3 (Chapter 4). Findings reported by Tays et al. (2008) showed that younger adults' N450 response was sensitive to interference effects from familiar stimuli and conflicting stimulus response mappings. However, evidence is lacking as to the precise nature of this cortical response as well as the specific roles of IFC and ACC therein. Activity in IFC is frequently associated with the resolution of interference and response control (e.g., Aron et al., 2004; Bunge, Ochsner, Desmond, Glover, & Gabrieli, 2001) while ACC activity is proposed to index response conflict (van Veen & Carter, 2002) or to signal the need for top-down control (Ridderinkhof et al., 2004; van Veen et al., 2002). Indeed, it may be that the N450 is a product of both of these fast acting systems; however, further exploration of the interference-related N450 is needed to advance our understanding of this issue.

In chapter 4, I describe an attempt to learn more about the precise nature of the N450 in young healthy adults by manipulating executive resources required to effectively deal with PI in working memory. The working memory load inherent in the

Sternberg task offered an easy means of manipulating the availability of executive resources. If the N450 reflects a neural response to conflict or serves as a signal for increased top-down control, then reducing executive resources should increase interference and magnify the N450 effect. However, if the N450 is an index of an adaptive response that reflects the active resolution of interference, then reducing executive resources should also reduce the N450. Beyond the main effects analyses of memory load on the magnitude of ERPs, source analysis of the N450 was also expected to produce information regarding the differing roles of ACC and right versus left IFC in supporting cognitive control. Thus, if the N450 in this task is an index of interference resolution, then as working memory load increases, and efficiency of interference resolution is reduced, some neural generators may show strong “conflict/need for control” activations while others may show specific “interference resolution” activations.

An additional issue investigated in Chapter 4 was the usefulness of signal decomposition from independent component analysis (ICA) and how it might allow a more focused analysis of the N450 effect. ICA may be particularly useful in dealing with the overlap of other ERP components co-occurring in time and topography with the N450. The P3b (or later positive component), in particular, presents a problem when measuring the N450 in the Sternberg task because the negative dipole of the P3b can project to frontal recording sites. Pairing the ICA with the working memory load manipulation was expected to provide a powerful test of the neural mechanism(s) underlying the N450 response.

Chapter 2

General Proactive Interference and the N450 Response

Published as:

Tays, W. J., Dywan, J., & Segalowitz, S. J. (2009). General proactive interference and the N450 response. *Neuroscience Letters*, 462, 239-243.

Abstract

Strategic repetition of verbal stimuli can effectively produce proactive interference (PI) effects in the Sternberg Working Memory Task. Unique fronto-cortical activation to PI-eliciting letter probes has been interpreted as reflecting brain responses to PI. However, the use of only a small set of stimuli (e.g., letters, digits) requires constant repetition of stimuli in both PI *and* baseline trials, potentially creating a general PI effect in all conditions. We used event-related potentials to examine general PI effects by contrasting the interference-related frontal N450 response in two Sternberg Tasks using a small versus large set size. We found that the N450 response differed significantly from baseline during the small set-size task only for response-conflict PI trials but not when PI was created solely from stimulus repetition. During the large set-size task N450 responses in both the familiarity-based and response-conflict PI conditions differed from baseline but not from each other. We conclude that the general stimulus repetition inherent in small set-size conditions can mask effects of familiarity-based PI and complicate the interpretation of any associated neural response.

Introduction

Efficient maintenance of the contents of working memory is central to complex decision-making, especially when one is confronted with competing sources of information. Proactive interference (PI), the disruption of behavior from the lingering influence of antecedent information, is long known to negatively impact the efficiency of both long-term (Underwood 1957) and short-term memory (Monsell 1978). The ability to resolve PI is important to working memory through its documented relation to overall memory span (Conway & Engel, 1994; Witney, Arnett, Driver, & Budd, 2001). Increased difficulty in resisting PI effects may also be a critical factor in cognitive aging as the representation of irrelevant stimuli hampers short-term storage and/or manipulation of behaviorally-relevant information, i.e., working memory (Darowski, Helder, Zacks, Hasher, & Hambrick, 2008).

Recent investigations into the neural basis of PI resolution in the Sternberg Task have indicated a prominent role for prefrontal cortex (Jonides & Nee, 2006). The Sternberg Task (Sternberg 1966) typically employs small memory sets of between 2 and 7 items per trial and a subsequent probe that is either a member (positive probe) or not a member (negative probe) of the current set. Critically, the Sternberg task has been used to study the neural basis of interference resolution using simple letter stimuli by strategically repeating negative probes from previous trials. In the first study of this kind, Jonides and colleagues (1998) found that recently repeated negative probes increased the likelihood of an erroneous positive response and elicited robust activation in inferior frontal gyrus (IFG), indicating that this region may be vital to PI resolution. Similar results have been reported for verbal stimuli (Badre & Wagner, 2005; but see

also (Mecklinger, Weber, Gunter, & Engle. Attempts have also been made to isolate the time-course of PI resolution using event-related potential (ERP) methods (Du, Xiao, Song, Wu, & Zhang, 2008; Tays, Dywan, Mathewson, & Segalowitz, 2008). The PI-related ERP component reported by Tays et al. (2008) was a frontal negativity at approximately 450 ms following PI probes (N450) with source-modeled generators in prefrontal cortex. This N450 has also been shown to relate to interference effects in variants of the Stroop task (West et al., 2004).

An assumption inherent in the methods described above is the engagement of particular brain processes in experimental trials and their absence in baseline/comparison trials. However, there are potential pitfalls when employing a subtraction method in psychophysiological research. The problems surrounding the use of an appropriate baseline in imaging studies are not new (Friston et al., 1996). Indeed, investigations of neural activity at rest have identified a possible ‘default mode’ that operates when participants have no explicit task (Raichle et al., 2001) and there is debate as to whether this profile of brain activation represents a useful baseline (Morcom & Fletcher, 2007). Issues regarding appropriate baselines have also been discussed with regards to ERP research (Newman, Twieg, & Carpenter, 2001; Van Boxtel 2004). For example, using difference waves will combine variance from both baseline and test conditions, which could diminish or exaggerate effects of interest.

We suggest that investigations of PI effects in the Sternberg task may suffer from this baseline problem. Specifically, in the case of the letter-based Sternberg Task the overall size of the stimulus pool could require the repeated presentation of previously seen letters in both experimental PI and negative (baseline) trials. For instance, a four-

item Sternberg task using 20 English letters over 360 trials would require every individual letter to be presented approximately 70 times aside from the particular experimental repetitions (Tays et al., 2008). Therefore, while a PI manipulation may be created by presenting a negative probe in the memory set of trial $n-1$, a non-recent negative probe (baseline) must have also been previously presented on other trials, e.g., $n-4$, $n-8$, etc. While the most recent repetition would be expected to show the strongest PI effect, it is unclear how more general stimulus repetition effects influence behavioral and neural responses to negative probes. If general PI effects are observed in young, healthy individuals, there may be even more powerful effects in special populations with specific problems with attentional control and interference resolution (e.g., older adults; Tays et al., 2008).

Our goal in the present study was to test the effects of generalized stimulus repetition by comparing ERP responses during two PI Sternberg Tasks: one using a small stimulus pool (20 common words), and another using a large stimulus pool (750 common words). We expected that using a small versus large stimulus pool would allow us to better dissociate neural responses due specifically to PI by reducing recency effects associated with negative (baseline) probes. This would demonstrate the degree to which generalized stimulus repetition creates a form of *general PI* that would have to be taken into account when interpreting psychophysiological evidence from such studies.

Methods

Participants

Participants were 21 Brock University undergraduates (15 women; 18-23 years, $M = 19.4$). All were right-handed, had normal or corrected-to-normal vision, and were

fluent English speakers. Exclusion criteria included self-reported neurological/psychiatric conditions or medications expected to affect neural function. Participants received research participation hours towards course credit or a small honorarium. The project received clearance from Brock University's Research Ethics Board and all participants gave written informed consent.

Experimental Design

Participants completed modified versions of the Sternberg task adopted from Tays and colleagues (2008). Stimuli were common three and four letter words drawn from the MRC Psycholinguistic Database (www.psy.uwa.edu.au/mrcdatabase/uwa_mrc.htm). The study was broken into two counterbalanced tasks. For one task (small set size), trials were created from a small test set of 20 three- and four-letter words.^{2,1} For the other task (large set size), trials were created from a large test set of approximately 750 three and four letter words, which allowed for only task-relevant repetitions.

As depicted in Figure 2.1, each trial began with a fixation cross at the centre of the screen for 500 ms. Next, four words in lowercase letters were presented in a box pattern around the fixation point. This display remained on screen for 1500 ms. The memory probe (in uppercase) appeared after a variable ISI between 1800 and 2400 ms. Participants indicated by a choice keypress (counterbalanced by response hand) whether this probe was a member of the target set associated with the current trial. There was a 1500 ms intertrial interval before onset of the next fixation cross. The probe was a member of the target set on 50% of trials (positive condition). The other 50% of trials were divided into four non-target conditions (negative, familiar, high familiar, and response conflict).

As can be seen in Table 2.1, during the negative condition, the probe did not match any of the four stimuli in the current or previous two target sets. When a large stimulus set is used, the negative probe will be presented only once throughout the entire task. However, when a small stimulus set is used, requiring general repetition, the current negative probe will have been seen on trial $n-3$, $n-4$, or $n-5$ (an example is seen in Table 2.1 as “edge” in trial $n-3$). In the familiar condition, a non-target probe in trial “ n ” had been in the target set of trial $n-1$. Any errors or increase in RT during these trials, relative to the negative condition, would reflect the added difficulty of overcoming PI effects from previous trials. The rationale for the highly familiar condition was similar to that of the familiar condition but with the current non-target probe appearing in target sets of trials “ $n-1$ ” and “ $n-2$ ”. In order to ensure that the presentation of an item in two consecutive memory sets was not conspicuous to the participant, every trial in both the large and small test sets had one item carry forward from the previous memory set. This can be seen in Table 2.1 for “kid” (in trial “ n ” and “ $n-1$ ”) as well as “link” (in trial “ $n-2$ ” and “ $n-3$ ”). Finally, on response conflict trials, the current negative probe had appeared as a positive probe on trial “ $n-1$ ” (an example is seen in Table 2.1 as “VOTE” on trial “ n ”). This manipulation was intended to add response-related PI effects, above and beyond the effect of familiarity. Each of the two Sternberg tasks included a total of 240 trials: 120 positive and 30 of each of the four non-target trials. Trials were divided amongst five blocks with each block separated by a short break and, for both tasks, testing began with 6 practice trials.

ERP Data Collection and Analysis

Participants were comfortably seated in a dimly lit, electrically and acoustically shielded room. Electroencephalogram scalp data were recorded using a 128-channel Geodesic Sensor Net (Electrical Geodesics, Eugene, OR) sampled at 500 Hz with a 0.1–100 Hz band-pass filter and vertex reference. Data were processed off-line with a 30-Hz low-pass filter and segmented into 1600-ms epochs (-600 to -400 ms baseline).^{2,2} Individual epochs were screened for noncephalic artifacts. Moderate eye artefacts were manually corrected using a program created in MATLAB studio (MathWorks, 2006) that removed the shared variance between bipolar eye channels and scalp electrodes. Epochs that remained were converted to an averaged ERP locked to the presentation of the probe, with an average reference, baseline corrected, and then combined to create group averages. Stimuli were presented using E-Prime research software (Psychological Software Tools, 2004) on a Dell VGA color monitor at an unfixed binocular distance of 60 cm from the participant.

All statistical analyses were corrected for violations of Mauchley's Test of Sphericity, where necessary, utilizing the Huynh-Feldt correction for estimating the F-Statistics; however, degrees of freedom are not adjusted in the text. Bonferroni multiple comparison corrections were used where appropriate. Mean RTs and accuracy data are based on correct trials only; RTs were trimmed by removing responses >3 standard deviations from individual participant means. To adjust for the spatial and temporal variability of N450 responses, ERP measures were combined over a cluster of six channels centered on AFz from 400-500 ms post-stimulus. One participant's data were

excluded from analysis due to continuous large movement artefacts during recording, so that analyses are based on data from 20 participants.

Results

Behavioral Data

Mean RTs to the negative and PI probes were analyzed in a 4 (condition) by 2 (set size) repeated measures ANOVA. There was a main effect of condition, $F(3, 57) = 51.27, p < .001, \eta^2 = .73$, and a main effect of set size, $F(1, 19) = 9.16, p < .01, \eta^2 = .33$, with no interaction, $F(3, 57) = .07, p = .97$. As can be seen in Figure 2.2a, RTs generally increased from the negative condition to the two types of familiar conditions, and then increased again in the response conflict condition. Whereas responses were faster during the small-set size task, likely due to priming effects, the overall pattern of condition effects did not differ between the two tasks. Error rates were analyzed in the same manner (Figure 2.2b). There was a main effect of condition, $F(3, 57) = 6.74, p < .01, \eta^2 = .26$, indicating a linear increase in error rate associated with increases in PI. There was no effect of set size, $F(1, 19) = .54, p = .47$, and no interaction, $F(3, 57) = 1.7, p = .18$. It is worth noting that the high familiar condition did not produce stronger interference effects than the single-repetition familiar condition; in fact, it produced numerically lower error rates and response time latencies.

Electrophysiological Data

Grand-averaged ERP waveforms associated with the negative and PI conditions are shown in Figure 2.3a and 2.3b. Visual inspection of waveforms shows an N450-like negativity in PI conditions, relative to negative, during both tasks. N450's appeared as part of a larger slow going negativity that did not systematically differ between the

negative and interference conditions that may reflect the anterior negative (di)pole of a posterior stimulus-locked P3b response to all probes (not analyzed in the present report). Of note, all conditions in the small set task appeared to have a negative shift from 400 to 500 ms relative to the conditions in the large set task. In fact the negative condition during the large set size task showed a slight positivity in this period. We tested these differences by creating an average N450 amplitude from 400 to 500 ms following the probe over the six-site cluster of frontal electrodes and submitted them to a 2 (set size) x 4 (condition) repeated measures ANOVA. There was a main effect of set size, $F(1, 19) = 25.84, p < .001, \eta^2 = .57$, such that the small set-size task produced a more negative N450 response in all conditions ($M_{\text{small-large}} = -1.38 \mu\text{V}, SE_{\text{diff}} = .31$).^{2,3} There was also a main effect of PI condition, $F(3, 57) = 13.04, p < .001, \eta^2 = .41$, however, this effect was qualified by a significant set size by condition interaction $F(3, 57) = 5.29, p < .05, \eta^2 = .22$. This interaction is seen when comparing the pattern of PI condition effects relative to baseline within each respective set-size (see Table 2.2). In line with our hypothesis, although PI effects for familiarity-based PI manipulations were in the expected direction for both tasks, the effects were significant only when a large set size was used. Interestingly, the response conflict PI effects were not influenced by the size of the stimulus set. This differential sensitivity of response-based vs familiarity based PI is consistent with accounts that identify separate neural mechanisms for the resolution of unique interference effects occurring at stages of response selection/execution (Nelson et al. 2003). Overall, the present results indicate that general PI inherent in the use of a small stimulus set reduces the effect of familiarity-based PI relative to the negative (baseline) condition.

Discussion

Attempts to examine the neural processes underlying interference resolution depend on the ability to dissociate those trials on which interference resolution is occurring from those on which it is not. We hypothesized that using a small stimulus set, thus requiring widespread stimulus repetition unrelated to experimental manipulations, would introduce *general PI* effects into the negative condition meant to serve as a non-PI baseline. Our data were consistent with this hypothesis in that there was an overall, long-lasting negative shift in the ERP responses to all negative probes in the small set size task, *including the baseline condition*. This may reflect the interference experienced by participants on every trial because of the high rate of stimulus repetition; indeed, by the end of the 240 trials every stimulus would have been presented approximately 40 times. As a result, the difference in N450 response between negative and experimental PI conditions was quite small when using a small set. In contrast, the large set size task, involving only deliberate repetition, resulted in a more substantial familiarity-based PI effect. In fact, under these conditions, the usual N450 amplitude difference between familiarity-based and response-based PI was no longer apparent in the ERP scalp response. This insensitivity of the N450 to the different interference conditions is somewhat surprising considering that the response conflict trials show stronger behavioral interference costs than familiarity-based interference. Imaging data has shown that response-based interference elicits unique activations in anterior cingulate cortex (ACC) (Nelson et al. 2003), while familiarity-based interference activates IFG (Jonides et al, 1998). It may be that the N450 is more reflective of activations from IFG than ACC, and therefore most sensitive to familiarity-based PI. Further research is

needed to identify the specific contribution of IFG and ACC response to electrophysiological correlates of PI. However, the critical point remains that if general PI effects from frequent stimulus repetition can undercut familiarity-based PI effects, the activations of brain regions contributing to these response, e.g., (Nelson et al., 2003; Tays et al., 2008), may also be underspecified.

The results reported here are not surprising considering that PI effects on behavior can be seen when items themselves are not repeated, but are drawn repeatedly from the same categories (e.g., letters or digits; Wickens, Born, & Allen, 1963). Recent neuroimaging work has demonstrated this category repetition effect, referred to as item-nonspecific PI, by testing the effect of trial position in the overall testing stream (Postle, Brush, & Nick, 2004). When trials occurred late in a particular block, they involved nonspecific PI effects on behavior and increased activation in left anterior IFG and left dorsolateral prefrontal cortex. The activation of dorsolateral prefrontal regions is particularly interesting because it occurs *in addition* to the typical activation of IFG consistently associated with short-latency, item-specific PI manipulations (Jonides et al., 2006).

The challenges involved in employing an appropriate baseline condition in psychophysiological research are not new (Newman et al., 2001), and more generally are central to the effective use of subtractive and additive factors methodology (Sternberg 1969). Of course, minimizing PI effects in a ‘baseline’ condition presents no small challenge; indeed, if common stimuli such as letters, words, or digits are used, there may be subtle PI effects operating from the outset of the first trial. Nonetheless, our findings demonstrate that the repetition inherent in the use of small stimulus sets can

introduce a confound in the negative (baseline) condition that results in an attenuation of PI-related brain responses to familiar probes. Alternatively, in the large set size condition, both response-based and familiarity based PI effects elicited robust brain responses to interference. This interpretive difference speaks to the importance of considering the larger task context that exists beyond the particular experimental manipulations of interest and emphasizes the need to carefully consider the processing demands associated with both experimental and baseline conditions.

Chapter 3

Age-Related Differences during Simple Working Memory Decisions: ERP Indices of Early Recognition and Compensation Failure

Abstract

Unique frontal cortical activation in older adults during simple recognition has been positively correlated with performance and could, therefore, be considered compensatory. However, in a previous electrophysiological study involving a Sternberg task with proactive interference manipulations, we observed a frontal positivity (400-500 ms) unique to older adults that was predictive of poorer performance. These results led us to ask whether unique frontal activation in older adults serves a compensatory role only during relatively simple tasks when stimulus familiarity provides an unambiguous basis for response selection. In the current study, we tested this hypothesis by having younger and older adults complete a verbal Sternberg task without interference manipulations. In younger adults, we observed an early posterior negativity (90-120 ms) that predicted performance accuracy. Older adults failed to show this early negativity but did produce the expected late frontal positivity. However, the late frontal positivity was again associated with poorer performance. These data support the view that younger adults are able to bias early target discrimination to benefit behaviour whereas older adults rely on later controlled processes that are not always effective in buffering against normative age-related decline.

Introduction

Aging has been associated with a shift in cortical activation from posterior to anterior brain regions (e.g., Davis, Dennis, Daselaar, Fleck, & Cabeza, 2008) and the bilateral frontal activation seen in older relative to younger adults during simple verbal and visual memory tasks has been thought to reflect compensatory processes that may serve to buffer cognitive functions in older adults from the full impact of normative neurophysiological decline (Cabeza et al., 2004; Grady et al., 1994; Gutchess et al., 2005; Madden et al., 1997; Rosen et al., 2002). In a recent study, Davis, Daselaar and Cabeza (2008) found that older adults with the most diminished activation in primary visual cortex on verbal memory and visual discrimination tasks (BA 17 and 18) showed the strongest activation in the middle frontal gyrus (BA 45). The strength of this shift from posterior to anterior activation was, in turn, positively related to behavioural performance. Such data constitute compelling evidence that unique frontal activation in older adults can compensate for age-related decline elsewhere in the brain.

We investigated these issues in a previous study (Tays et al., 2008) in which high density EEG was recorded while younger and older adults completed a modified delay-to-match Sternberg task with proactive interference manipulations. We found that younger adults produced a robust, interference-related frontal N450 response (see Markela-Lerenc et al., 2004; West et al., 2004) whereas older adults produced a diffuse positivity over frontal recording sites in all conditions. Because older adults, as a group, performed the task nearly as well as younger adults, this activation (referred to here as the late frontal positivity) was initially hypothesized to reflect compensatory processes.

However, analysis of individual differences within the older group indicated that larger late frontal positivities actually related to poorer behavioral performance.

Although these findings were not consistent with a compensation account, they were in line with other research showing that unique cortical activity in older adults, ostensibly similar to that observed in studies supporting a compensatory interpretation, can also predict poorer performance (e.g., Langenecker & Nielson, 2003; Logan et al., 2002). As an example, Colcombe, Kramer, Erickson, and Scalf (2005) took fMRI recordings during an interference-inducing perceptual flanker task wherein participants were required to suppress prepotent responses to distracting adjacent stimuli. They found that additional left frontal activation in older adults relative to the typically more focal, right frontal activation in younger adults was indicative of reduced accuracy. Thus, it appears that bilateral frontal activity in older adults is not universally compensatory and that the factors determining whether unique fronto-cortical activation is a sign of compensation, as opposed to cognitive decline, remain unclear.

Examining the time course of information processing in the Tays et al. (2008) study, we also noted that younger adults appeared to discriminate targets from non-targets much earlier than the older adults. A frontal P3a response was larger for targets than nontargets in the younger group, suggesting that target discrimination had occurred by approximately 300 ms. Older adults showed no evidence of such discrimination until 500-600 ms post probe when they produced a posterior P3b response (i.e., a parietal old/new effect) which was, of course, highly robust in the younger group as well. The failure of older adults to show this early cortical discrimination supported the view that older adults rely more heavily on later, controlled decision processes occurring closer to

the point of response selection (Jacoby et al., 2005; Jacoby, Kelley, & McElree, 1999). One could further speculate that failed early discrimination in older adults leads to unique frontal activation, possibly reflecting later occurring attempts to recruit additional controlled processing to aid performance. However, the observation of an inverse relationship with behavioural performance would suggest that this additional controlled processing is not always sufficient to overcome declining functions, especially in contexts where interference must be resolved.

One important methodological difference between studies that have supported the compensation account (e.g., Cabeza et al., 2002; Park et al., 2003; Reuter-Lorenz 2002) and those that have not (e.g., Colcombe et al., 2005; Langenecker et al., 2003; Tays et al., 2008) was the inclusion of interference conditions that required participants to withhold a prepotent response to salient lures. It may be that compensatory processes are effective only during tasks requiring relatively simple recognition memory decisions that, in turn, rely on judgments of familiarity. The tendency of older adults to fall victim to indiscriminant attentional capture by familiar, and therefore, salient stimuli (Jacoby et al., 1999) may not compromise behavioural performance during such simple recognition memory tasks. However, the same attentional capture in a task that requires the ability to override the salience of nontarget stimuli or “lures” would place extra demands on controlled processing and be particularly difficult for older adults to overcome. In the flanker task used by Colcombe et al. (2005) and the go/no-go task used by Langenecker and Nielson (2003), the ability to countermand prepotent response tendencies was central to task performance. Similarly, in the Tays et al. (2008) task, familiar non-target probes would capture attention in ways that would compromise task performance unless

cognitive control mechanisms could be effectively employed to discriminate the familiarity associated with targets from that associated with non-target lures.

If interference manipulations in the modified Sternberg task discussed above were removed, it would make target discrimination easier for both younger and older adults because participants could rely on stimulus familiarity for memory decisions. This change in task demands could result in two potential effects observable in participants' cortical response to probes. First, the early target discrimination observed in young adults may be even more evident than reported by Tays et al. (2008). In fact, past research has identified such effects within the first 200 ms of stimulus processing (see Agam et al., 2009; Fenske, Aminoff, Gronau, & Bar, 2006; Rutman, Clapp, Chadick, & Gazzaley, 2010). Second, in older adults, performance may be enhanced, rather than impaired, as a function of familiarity-based attentional capture. However, due to age-related decline in early, automatic processes (Alain, McDonald, Ostroff, & Schneider, 2004; Jacoby et al., 1999), the response to this familiarity would be evident at a relatively late stage of information processing, such as during the late frontal positivity or even later (see Wolk et al., 2009). Such results would be consistent with Daselaar and colleagues' (2006) findings that increased functional connectivity between frontal and rhinal cortices aided the processing of familiarity traces.

Thus, in a context in which familiarity consistently serves to benefit goal-directed behaviour, such boosting of recognition signals could arguably serve a compensatory function. If the late frontal positivity observed in Tays et al. (2008) is sensitive to some aspect of familiarity processing, then removal of interference trials could result in a positive relationship between this unique frontal activation in older adults and their

behavioural performance. Moreover, since electrophysiological measures grant important information on the time-course of cognitive processes proposed to influence behaviour, such a finding would be complimentary to the existing literature on compensatory activation in older adults, which relies heavily on imaging data.

The present study was designed to examine the beneficial effect of familiarity on simple memory decisions and its influence on early versus late stages of information processing revealed by electrophysiological recordings in younger and older adults. We used a simple Sternberg task without salient non-target probes to elicit recognition memory decisions over very brief delay periods. In order to test age-effects over longer delays, we also included a secondary task measuring incidental memory of Sternberg probes to provide a measure of familiarity-based long-term memory judgments (see Figure 3.1 for a graphic depiction of these tasks). In both tasks, older adults were expected to produce late frontal activation in response to familiar relative to non-familiar target probes and the amplitude of this activation was expected to relate to higher levels of accuracy. As well, younger adults were expected to show unique sensitivity to old versus new probes much earlier than older adults, and this early sensitivity should also be associated with better task performance.

Method

Participants

Twenty younger adults (14 female; 18-24 years, $M = 20.1$, $SD = 1.7$) and 18 older adults (10 female; 64-79 years, $M = 71$, $SD = 4.7$) took part in the study. Participants were right handed, had normal or corrected-to-normal vision, and were fluent in English. Exclusion criteria included neurological/psychiatric disorder or

medications expected to affect neural function. Older participants completed the Mini-Mental Status Examination (Folstein, Folstein, & McHugh, 1975) and all scored within the normal range (26-30, $M = 28.6$, $SD = 1.1$). All participants completed the SCOLP verbal processing task (Baddeley, Emslie, & Nimmo-Smith, 1992), revealing a typical vocabulary superiority effect for older ($M = 51$, $SD = 6.7$) versus younger adults ($M = 46$, $SD = 5.6$), $t(36) = 2.46$, $p < .05$. Participants received research participation hours towards course credit or a small honorarium. The project received clearance from Brock University's Research Ethics Board and all participants gave informed consent.

Materials and Procedure

This study was conducted as part of a larger project on aging, motor control, and cardiac function. Graphic representations of the tasks reported here are presented in Figure 3.1. For the simple Sternberg task, stimuli consisted of common three and four letter words drawn from the MRC Psycholinguistic Database (www.psy.uwa.edu.au/mrcdatabase/uwa_mrc.htm). They were presented on a 17 inch CRT monitor using E-Prime (Psychological Software Tools, 2004) and appeared in white font on a teal background. Probe stimuli subtended a visual angle of 2.3 degrees at a distance of 50 cm. At the beginning of each trial, a fixation cross appeared at the centre of the screen for 1000 ms. Next a memory set of four words in lower case were displayed for 2000 ms in a box pattern around fixation. A retention interval of between 2800-3600 ms preceded the presentation of a probe word in capital letters, which was presented for 1000 ms followed by a 500 ms blank screen. The probe matched an item in the memory set on 50% of trials. Participants indicated whether the probe was old or new via a speeded two-choice button press. A total of 80 trials were presented as two

40-trial, pseudo-randomized blocks and participants were randomly assigned to complete one of two versions of the task wherein old probes in one version served as new items in the other. No stimuli were repeated within the task.

Following the simple Sternberg task, there was a surprise test of incidental learning of Sternberg task probes (both old and new). This required familiarity-based recognition memory judgements and included no interference from stimulus repetition. Test stimuli (one Sternberg probe and one entirely new item) were presented in pairs but displayed serially in randomized order; this allowed each probe and new item to produce a discrete ERP. Each of the two stimuli were presented for 1500 ms and separated by a 1000 ms blank screen before an unlimited-duration cue appeared, signalling the participant to make a response. Participants indicated by key press whether the first or second stimulus was the target. There were a total of 80 pseudo-randomized trials, one for each previous Sternberg probe.

ERP Data Collection and Analysis

Participants were comfortably seated in a dimly lit, electrically and acoustically shielded room while EEG was collected using a 128-channel Active Two Biosemi system (BioSemi, Amsterdam). Eye-movements were recorded with three electrodes placed on the outer canthus, supra-orbital ridge, and cheekbone of the right eye. Signals were sampled at 512 Hz and digitized with a 24 bit ADC. The BioSemi system does A-D conversion at the electrode site so that the amplifier gain was 1. Data were processed off-line with a 30 Hz low-pass filter (12 dB/oct roll-off) and data for correct trials were segmented into 1200-ms epochs (-200 to 0 ms baseline). Individual epochs were screened for noncephalic artifacts. Moderate vertical eye artifacts were corrected using a

program created in MATLAB (MathWorks, 2006) that removed the shared variance between bipolar eye channels and scalp electrodes. Epochs that remained were converted to an averaged ERP, with an average reference, and then combined to create group averages. We report the names of sensor electrodes by approximating to the extended 10/20 sensor layout.

All statistical analyses were corrected for violations of Mauchley's Test of Sphericity, where necessary, utilizing the Huynh-Feldt correction for estimating the F-Statistics; however, degrees of freedom are not adjusted in the text. Mean RTs are based on correct trials only and trimmed of responses that occurred more than 3 standard deviations from individual subject means.

Results

Behavioral data

Mean percent accuracy and response times (RTs) for the Sternberg and incidental memory tasks are presented in Table 3.1. Mean RTs to the old and new probes in the Sternberg task were analyzed in a 2 (probe type) by 2 (age group) repeated measures ANOVA. There was a robust effect of age group, $F(1, 36) = 18.20, p < .001, \eta^2 = .37$, such that older adults responded on average 165 ms slower than younger adults but there was no effect of probe-type or interaction (both $F_s < 1$). Sternberg task accuracy was analyzed in a similar fashion indicating a main effect of probe type, $F(1, 36) = 4.21, p < .05, \eta^2 = .10$, whereby new probes elicited a higher rate of correct responses than old probes, but there was no effect of age group or interaction (both $F_s < 1$). Whereas our accuracy data may be subject to ceiling effects in the Sternberg task, it is, nonetheless,

clear that both groups were able to complete the task with little difficulty, albeit with the expected age-related slowing in the older group.

Although the majority of participants reported high rates of guessing on the incidental memory task, accuracy rates in both groups were above chance (see Table 3.1). Given that responses were not speeded and base accuracy rate due to chance was 50%, an estimate of the proportion of recognized probes could be calculated as $(\text{Accuracy} - \text{Chance}) / (1 - \text{Chance})$. Accuracy rates were 71.2% (42.4% estimated probe recognition) for younger adults and 63.8% (27.6% estimated probe recognition) for the older group revealing a higher recognition rate in younger versus older adults, $t(36) = 2.63, p < .05$. Since participants were instructed to withhold responses until a cue appeared, there are no meaningful RTs in this task.

Electrophysiological Data

Grand-averaged, stimulus-locked ERP waveforms to correctly identified old and new Sternberg probes for younger and older participants are shown in Figure 3.2a. Visual inspection revealed three effects associated with our hypotheses (see Table 3.2 for the associated key mean amplitudes).

Sternberg Task. The first effect of condition was a conspicuous negativity over occipital sites at around 100 ms following the probe (referred to here as the early posterior negativity) with a duration of approximately 20 ms when viewed in individual subject data (see Figure 3.3 for early posterior negativity topography). This component was measured as the peak negativity at POz between 90 and 120 ms after the probe and entered into a 2 (probe type) by 2 (age group) mixed-model ANOVA that revealed a trend towards an condition by group interaction, $F(1, 36) = 3.2, p = .08, \eta^2 = .08$. A

simple effects analysis in each age group indicated an effect of condition, $F(1, 19) = 4.21, p < .05, \eta^2 = .10$, for young adults, suggesting a very early sensitivity to old versus new items, an effect not observed in the older group ($F < 1$). Latency of the early posterior negativity was analyzed in like fashion but revealed no effect of condition, group, or interaction (all F s < 1.3).

Average P3b amplitudes at Pz were measured from 350-600 ms after the probe. A 2 (probe type) x 2 (age group) ANOVA revealed a significant interaction, $F(1, 36) = 41.01, p < .001, \eta^2 = .53$, with subsequent analyses indicating a greater amplitude on the part of younger adults to old relative to new items, $F(1, 19) = 41.80, p < .001, \eta^2 = .69$, a sensitivity that was present but less robust in the older group, $F(1, 19) = 8.25, p < .05, \eta^2 = .33$.

Of specific concern was the unique positivity over frontal recording sites evident in the waveforms of older adults. It showed a similar, but slightly more lateralized topography and a somewhat earlier time-course to that observed in our previous study (Tays et al., 2008). Given that younger adults produced no late frontal positive component, and the potential overlap of the negative (di)pole of their P3b, we focus only on the older adult data (see topography in Figure 3.3). A repeated measures t-test based on the average amplitude at AFz from 350-450 ms after the probe revealed no sensitivity to condition, $t(1, 17) = .72$, n.s. Thus, although the present task allowed for beneficial effects of familiarity, the late frontal positivity did not show sensitivity to probe type.

Incidental Memory. The incidental memory test also elicited a P3b in response to old relative to new items but no early discrimination was evident for either group (see

Figure 3.2b). This P3b was averaged over Pz from 450-650 ms following probe stimuli and a 2 (probe-type) by 2 (age group) ANOVA confirmed that the old items did elicit a larger P3b than new items, $F(1, 36) = 9.13, p < .01, \eta^2 = .20$, and that the P3b was larger in young relative to older adults, $F(1, 136) = 14.35, p < .001, \eta^2 = .29$. Although the waveforms of older adults as a group actually showed a slight difference in the opposite direction that that seen in the young, the test of the interaction did not reach significance, $F(1, 36) = 2.59, p = .12$.^{3.1}

In the incidental memory task older adults produced what appeared to be unique late frontal positive potentials over a similar time frame as observed for the Sternberg task, although the topography was limited to a small area over right frontal sites. This positivity at FP2, maximal from 325 to 425 ms after probes, appeared to be larger for old items relative to new items but a repeated measures t-test found no reliable difference, $t(17) = 1.41, p = .18$. Again, younger adults showed a modest negative deflection in this time period, likely the inverse (di)pole of the P3b.

Relationships among dependent variables

Pearson correlations were conducted separately for each group. We first explored the relationship between the behavioural performance (i.e., memory accuracy) on the two tasks. Younger adults' performance did not reliably relate across tasks ($r = .29, p = .21$), though it was in the expected direction. In contrast, there was a clear association across tasks for older adults ($r = .72, p < .001$). We also found that Mini-Mental Status Examination (MMSE) scores were inversely related to older adults' incidental memory task accuracy ($r = -.54, p < .05$), but not Sternberg task accuracy or RT (p -values $> .30$),

but showed no relationship to the late frontal positivity measure in either task (p -values $> .28$).

Of central interest was the relationship between older adults' late frontal positivity and their behavioural performance on the memory tasks. By having excluded proactive interference effects, we hoped that probe familiarity would facilitate accurate memory recognition and expected that larger frontal positivities would, in this case, relate to better memory performance across the tasks. As in Tays et al. (2008) we used a measure of the average late frontal positivity across conditions, but found that the mean was, once again, inversely related to accuracy in the Sternberg task ($r = -.48$, $p < .05$; for scatter plot, see Figure 3.4). Thus, these results failed to support our hypothesis that, by removing interference manipulations, we would find that larger late frontal positivities would predict higher levels of recognition memory performance in older adults. In fact, our results replicated our previous observation, i.e., that the age-specific late frontal positivity was associated with an increase rather than a decrease in error rate.^{3.2} The late frontal positivity observed in the incidental memory task also tended towards a negative correlation with accuracy but this pattern was not statistically reliable ($r = -.27$, $p = .28$). We are, therefore, forced to conclude that being able to rely heavily on the general familiarity of an item for accurate target selection is not a mediator of the relationship between the late frontal positivity in older adults and their subsequent memory decision.

Finally, we examined the relationship of the early posterior negativity to behavioural performance in the Sternberg task to determine if this very early cortical response in younger adults could predict the accuracy and speed of their behavioural responses. To do this, we calculated the standardized residual amplitude of participants'

response to old probes by removing shared variance associated with response to new probes through linear regression. In this case, more negative values represent a greater sensitivity to old items (i.e., a relatively larger early posterior negativity to old probes adjusted for the amplitude to new probes). We correlated this residual with average Sternberg task accuracy and found an inverse relationship ($r = -.46$, $p < .05$; see Figure 3.5a), such that greater sensitivity to old probes predicted higher levels of accuracy. We also examined the relation of the residualized early posterior negativity with average behavioural RT and found an inverse relationship ($r = -.62$, $p < .01$; see Figure 3.5b), such that greater sensitivity to old probes was associated with shorter response times. Together, these findings reveal that younger adults can show very early discrimination (i.e., within 100 ms) between probes that match items stored in working memory and those that do not and that the ability to make this discrimination has positive implications for performance.

Discussion

Younger and older adults completed a simple Sternberg task to determine whether a context that benefited general, familiarity-based memory decisions would enhance target sensitivity in the early cortical response of younger adults and reverse the negative relationship between the unique late frontal positivity in older adults and their behavioural performance. ERP recordings in young adults revealed a surprisingly early sensitivity to targets versus non-targets as seen in a negativity over occipital recording sites at approximately 100 ms following the probe (referred to here as the early posterior negativity). Importantly, the degree of amplitude sensitivity in this component (larger negativity to old relative to new items) was associated with overall memory accuracy

and speed of response. Although older adults did not produce this early posterior negativity, they, like the younger adults, did produce a robust P3b component showing cortical discrimination of targets versus non-targets but at a relatively late stage of processing. These findings provide further support for the perspective that younger adults are able to rely on early and relatively automatic target discrimination during simple memory judgments, whereas older adults must rely on later, more controlled processing (Alain et al., 2004; Jacoby et al., 1999; Tays et al., 2008).

In a subsequent incidental memory task, younger adults showed better recognition memory for the previously-presented Sternberg probes than older adults. They also produced a reliable parietal old/new effect (P3b) not observed in the older sample for this task. Although cognitive status, as indexed by the MMSE, was positively related to behavioural performance, there was no evidence that the modest late frontal positivity produced by older adults in the incidental memory task was linked to their recognition accuracy.

We expected that early cortical sensitivity to old probes would be evident for younger adults in the Sternberg task but did not specifically predict the early posterior negativity effect, so this finding awaits replication and should be interpreted with caution. We note, however, the longstanding evidence that voluntary efferent control can influence early sensory processing (e.g., Corbetta, Miezin, Dobmeyer, Shulman, & Petersen, 1990; Hillyard & Mangun, 1987). Using ERPs, Foxe and Simpson (2002) showed robust activation for visual stimuli in occipital cortex around 50 ms and robust dorsolateral frontal activations within 80 ms, giving ample time for re-efferent signals to bias ongoing posterior perceptual processes. Moreover, Fenske, Aminoff, Gronau and

Bar (2006) suggest that early, low resolution signals are carried by the magnocellular pathway (Kveraga, Boshyan, & Bar, 2007) and, once reaching prefrontal regions, re-efferent signals can quickly communicate with posterior sensory areas to bias processing (Bar et al., 2006; Corbetta & Shulman, 2002).

We note, as well, that top-down sensitivity to target stimuli may be enhanced in the Sternberg task because the four main stimuli that could appear as subsequent positive probes are maintained in working memory during each trial. Therefore, the top-down mechanisms described above may establish a pre-emptive sensitivity in posterior sensory cortex to the four possible old items before the probe even appears. A similar effect has been reported by Agam et al. (2009) who required sinusoidal luminance gratings to be held in working memory while high-density EEG was recorded. Their participants showed perceptual processing sensitivity to probe identity over occipital sites by 156 ms and this was thought to reflect a memory comparison function between probe items and items held in visual short term memory. Our early posterior negativity effect was even earlier than the 156 ms reported above, but Agam et al. (2009) note that their finding does not represent the earliest possible point of probe discrimination. Moreover, the multidimensional nature of verbal stimuli, as used in the present Sternberg task, may provide a particularly effective means for exerting a rapid top-down influence (see Allen, Smith, Lien, Kaut, & Canfield, 2009; Lupyan, Thompson-Schill, & Swingley, 2010).

Whereas younger adults show evidence of an early target identification mechanism, as seen in Tays et al. (2008) and again in the present study, this mechanism is not operant in older adults. This finding is consistent with the view that aging

involves a decline in the efficiency of early target discrimination (Alain et al., 2004; Gazzaley et al., 2008; Jacoby et al., 2005; Tays et al., 2008) thus requiring older adults to depend on later, more controlled processing to meet tasks demands. Whereas this can allow nearly equivalent performance to younger adults on simple tasks, it may come at the cost of exacerbating response-time differences between older and younger adults and be reflected in the age-specific extensive fronto-cortical activation during simple cognitive (e.g., Fabiani, Friedman, & Cheng, 1998) and motor control tasks (e.g., Heuninckx, Wenderoth, Debaere, Peeters, & Swinnen, 2005)..

Of central relevance, we observed this fronto-cortical activation in the form of a late frontal positivity that was unique to our older adults, a replication of the ERP component reported by Tays et al. (2008). Despite the removal of familiarity-based interference, the component's amplitude was not sensitive to old versus new probes and the late frontal positivity was once again inversely related to the overall accuracy of memory judgments in older adults. This result suggests that the presence or absence of interference manipulations does not mediate the relationship between the late frontal positivity and accuracy for older adults during the Sternberg working memory task.

At first blush, this pattern of relationship would suggest that the cortical activation reflected in the late frontal positivity is an index of maladaptive or nonselective cortical recruitment (see Logan et al., 2002, for evidence of nonselective activation evoked during particular task demands). However, we cannot necessarily conclude from this correlation that the frontal positivity indexes some process that, itself, impairs performance. Indeed, Langenecker and Nielson (2003) suggest that unique frontal activation in older adults during their go/no go task may be compensatory but not

always sufficiently effective to overcome other factors associated with an age-related decline in performance. Colcombe et al. (2005) also emphasize that the relationship between unique cortical recruitment and behaviour will depend on whether the resources recruited can aid performance under the given task demands. Therefore, if additional recruitment is intended to aid performance but the recruited resources are insufficient or inappropriate in meeting task demands, participants will make performance errors (i.e., the attempt to compensate fails).

Functional imaging studies have been most supportive of a compensation account for unique frontal activations but, even here, the relationship between brain activation and behaviour is inconsistent. For instance, in a divided-field visual attention study using fMRI, Solbakk et al. (2008) measured brain responses in younger and older adults for infrequent attended targets and unattended novelties in a stream of standards. Both groups showed broad cortical recruitment, with younger adults relying most heavily on posterior areas while older adults showed relatively more reliance on frontal areas. Critically, older adults with the broadest frontal activation showed the poorest behavioural performance. Therefore, the spatial extent or breadth of fronto-cortical recruitment was a sign of decline in older adults.

Electrophysiological data has been less prominent than imaging data in advancing the compensation debate but several studies provide examples consistent with the compensation failure account. Research documenting the frontal shift in the ERP topographies of older adults (see Friedman 2003 for a review of several seminal studies) supports the view that effortful frontal recruitment is required to deal with the deleterious effects of aging. For example, during the oddball task older adults produce

more anteriorly-distributed P3 responses to targets and the extent of this frontal shift predicts poor performance on standardized neuropsychological tests, particularly the Wisconsin Card Sorting Task (Fabiani et al., 1998). The extent of the frontal shift in the parietal old/new effect during recognition memory judgments also co-occurs with performance declines (e.g., Walhovd et al., 2006). Additionally, Wolke et al. (2009) showed that older adults who failed to make old/new discriminations in the parietal late positive component produced an additional broad-ranging positivity over frontal sites between 800-1200 ms after a memory probe. These authors suggest that this late-occurring positivity may be similar to the unique activations documented in functional imaging studies, and may reflect late-occurring controlled processing attempts to aid retrieval. However, older adults showing the greatest extent of hyperfrontality also showed the poorest memory performance.

In summary, older adults can show nearly equivalent behavioural accuracy to younger adults across a variety of task demands. However, this level of performance likely comes at the cost of employing slower, more controlled processing that can be observed as greater frontal brain activation. On the one hand, this relatively late controlled activation could be viewed as compensatory because it could reflect attempts to aid goal-directed behaviour. On the other, the need to recruit additional controlled processing is an overall sign of reduced neural efficiency. As Friedman (2003) reflects, “One scientist’s compensation is another’s inefficiency” (p. 715).

Dealing with this problem of interpretation can be aided first by considering individual differences within age groups, as has been done here, or by dividing older adults into high-performers and low performers (e.g., Cabeza et al., 2002). Furthermore,

using an additive factors model, such as varying the working memory load, may uncover similar relationships in younger adults if they are pushed to the limits of their performance (see Schneider-Garces et al., 2010). Advances in signal processing techniques have also made it possible to study information processing at the level of the individual trial in both fMRI and ERP recordings (e.g., Debener, Ullsperger, Siegel, & Engel, 2006) which may additionally benefit from data mining algorithms like independent component analysis (Eichele, Calhoun, & Debener, 2009; Makeig, Debener, Onton, & Delorme, 2004). Future research may show that, whereas mean levels of activation in the frontal positivity represent a general measure of decline in older adults, activation measured at the level of the individual trial may predict a successful memory decision.

Chapter 4
Interference Detection or Resolution?
Delineating the Time Course and Function of the N450 with Cognitive Load and Independent Component Analysis

Abstract

Using event-related potentials (ERPs) to examine neural responses to proactive interference (PI) has consistently revealed a medial frontal negativity 450 ms following interference eliciting stimuli. However, it is unclear whether this N450 reflects PI detection or PI resolution. Our goal was to probe the nature of the processes that give rise to this N450 by manipulating cognitive load, thus limiting available executive resources. We elicited PI by using a modified Sternberg task that involved the strategic repetition of recent probes. Cognitive load was manipulated by using 2, 4, & 6 items in the memory set. We hypothesized that PI effects would increase with greater cognitive load. If the N450 reflects PI detection, its amplitude should increase as load (and thus PI) increases. Alternatively, if the N450 reflects PI resolution, its amplitude should decrease as load increases and executive resources become limited. Behavioural data supported a clear pattern of increased PI; errors to lures increased linearly with load. ERP data were surprising in that two PI-related negativities were observed. At low load (maximal resources available) a left-frontal negativity occurred, while at high load (minimal resources available) a right-frontal negativity was apparent. We suggest that the typically observed N450 is actually a composite of two functionally distinct responses: A right-lateralized response reflecting interference detection or a general stop-signal, and a left-lateralized response reflecting the application of executive resources for interference resolution.

Introduction

Selective attention is a fundamental aspect of information processing that allows for an intention-driven focus on goal-relevant information. However, due to the limited capacity of cognitive resources, attentional capture by non-relevant information can result in considerable costs to goal-directed behaviour. The cognitive processes that serve to detect, withstand, or resolve such interference, have received considerable study (e.g., Badre & Wagner, 2004; Botvinick et al., 2001; Egner, Delano, & Hirsch, 2007; Nee, Jonides, & Berman, 2007; Ridderinkhof, van den Wildenberg, Segalowitz, & Carter, 2004) and converging evidence has shown that both medial and lateral prefrontal cortex (PFC) are key to implementing these functions (Aron et al., 2004; Badre & Wagner, 2005; Chambers et al., 2006; Derrfuss, Brass, Neumann, & von Cramon, 2005; Egner et al., 2007; Nelson, Reuter-Lorenz, Persson, Sylvester, & Jonides, 2009; Ridderinkhof et al., 2004). However, although regions of PFC have been shown to play a central role in monitoring and adjusting both attention-driven sensory input and goal-driven behavioural output (e.g., Amiez et al., 2006; Badre et al., 2005; Fan et al., 2008; Rushworth et al., 2004), the specific neuro-cognitive mechanisms supporting these varied processes are not well understood.

In a previous study from our own lab, we recorded event-related potential (ERP) responses as younger and older adults reacted to familiarity-based and response-based interference in a modified Sternberg task (Tays et al., 2008). For each trial a memory set of 4 letters was presented followed by a letter probe. Participants were required to indicate by key press whether the probe had been part of the memory set. The familiar interference condition was created by having presented a current probe in the previous

(n-1), or two previous (n-1 & n-2) trials. Additional response-related interference was created by presenting a probe not currently in the target set, but which had been a target probe on the previous trial (n-1). Nelson and colleagues (Nelson et al., 2003), who initially developed this task for a functional magnetic resonance imaging (fMRI) study, had reported that familiarity-based interference was associated with activation in the left inferior frontal gyrus (IFG) whereas response-based interference produced additional activation in the anterior cingulate cortex (ACC), thus making a distinction between the neurocognitive mechanisms underlying cognitive control.

The electrophysiological data from the Tays et al. (2008) study revealed a medial frontal negativity occurring between 400-500 ms in response to the familiar and response-conflict Sternberg probes, a component referred to as the interference-related N450. N450 topographies and latencies were similar between the two interference conditions, but with response-based interference eliciting the numerically largest N450. Using Brain Electrical Source Analysis (BESA), the N450 was found to be best modeled by generators in the dorsal ACC and to left and right inferior frontal cortex (IFC). These findings implicated the same regions as reported by Nelson and colleagues (2003) and roughly mirrored other electrophysiological research on cognitive control in the Stroop task (Markela-Lerenc et al., 2004; Rebai, Bernard, & Lannou, 1997; West & Alain, 1999; West et al., 2004). For example, West, Bowry and McConville (2004) investigated activations associated with response-eligible and response-ineligible incongruent conditions in a counting Stroop task, which required participants to respond to the number of digits presented (e.g., 7 7 7) and ignore the digit's identity. Response eligibility was also dependent on the presence of specific response-related interference

effects additive to interference from stimulus identity. An N450 was observed in response to both types of interference trials relative to neutral trials and was largest for the more difficult incongruent eligible trials. Localization placed the related dipoles in ACC and anterior PFC. Thus, with some variation in amplitude and topography, a clear N450 could be observed under conditions of both response-related and nonresponse-related interference.

Results from Tays et al. (2008) and studies using the Stroop variants mentioned above were taken as evidence that ACC and IFC are both involved in supporting the general cognitive control processes required in response to multiple forms of interference. However, this association between the interference manipulations and the N450 (as well as functional indices of homologous activations) gives little indication of the precise cognitive process it reflects. There is some suggestion that the N450 reflects an interference detection process (West, 2003) during the Stroop tasks. However, while this notion is consistent with the view of the ACC as a conflict detector (Botvinick et al., 2001), a direct test of this model of the N450 is still needed.

The goal for the current study was to further specify the neurocognitive mechanism(s) that influence the amplitude and latency of the N450 seen at the scalp. The central question was whether the N450 reflects the monitoring of interference/conflict (i.e., a reflexively elicited process) or interference resolution (i.e., an actively recruited process). While both of these processes would require the active maintenance of task-demands, the mechanisms by which they operate may offer a means dissociation. This division is a useful starting place for identifying the mechanism underlying the N450 because responses to interference should require a two-

stage response at minimum: an initial detection of the need for cognitive control and the exertion of cognitive control to bring behaviour in line with intention.

The initial detection stage of cognitive control could include identifying interference between internal mental processes (such as reading the colour word instead of identifying the ink colour in a classic Stroop task) or conflict in the execution of motor responses (such as initiating a button-press during a withhold trial in a no-go task). Such functions are often considered under the general domain of “performance monitoring”, i.e., the ongoing surveillance of internal states and behaviour to detect instances of mismatch between current performance and the expectations determined by task demands. This could involve a diverse family of functions geared towards determining both the appropriateness of cognitive states and of behavioural output, all of which are typically associated with medial, as opposed to lateral, PFC functions (Ridderinkhof et al., 2004; Ridderinkhof et al., 2004). In this regard, the role of ACC in performance monitoring has received a great deal of attention, although attempts to specify its functions have led to debate. For instance, Conflict Monitoring Theory (Botvinick, Braver, Barch, Carter, & Cohen, 2001; Jones, Cho, Nystrom, Cohen, & Braver, 2002) posits a conflict detection role for the ACC specific to interference at the level of response selection. Although many researchers have reported evidence consistent with ACC sensitivity to response selection (e.g., Kerns et al., 2004; MacDonald, Cohen, Stenger, & Carter, 2000; Milham, Banich, & Barad, 2003; Milham et al., 2001), it is clear that ACC plays a broader role in cognitive control and performance monitoring involving such processes as reward encoding (Amiez et al., 2006), adaptive decision making (Kennerley, Walton, Behrens, Buckley, & Rushworth,

2006; Walton, Croxson, Behrens, Kennerley, & Rushworth, 2007), and subgoal integration of actions & information (Badre et al., 2004).

Interference resolution, presumably supported by both lateral and medial PFC, is thought to involve top-down control following signals from performance monitoring systems in order to maintain goal-directed behaviour. Several processes may be involved. These mechanisms include biasing-signals generated in PFC that facilitate or inhibit the processing of information in posterior sensory cortices (Crottaz-Herbette & Menon, 2006; Gazzaley & D'Esposito, 2007; Milham et al., 2001; Weissman, Gopalakrishnan, Hazlett, & Woldorf, 2005), the refreshing of internal representations to overcome effects of distracters (Brass & von Cramon, 2002; Derrfuss, Brass, Neumann, & von Cramon, 2005; Derrfuss, Brass, & von Cramon, 2004), or the maintenance and/or updating of representations of task context, such as abstract rules and stimulus contingencies (Braver et al., 2001; West & Alain, 2000).

The isolation of interference detection and interference resolution, either of which may be reflected in the N450 elicited by various Stroop and Sternberg interference manipulations, requires a dissociation of processes. Whereas brain-behaviour correlations (as seen in the fMRI and ERP studies mentioned above) show consistent functional links between PFC and behavioural response to interference, it is difficult to distinguish the initial detection of interference from the top-down control processes that overcome the interference and adjust for the desired response. Indeed, an individual experiencing high levels of interference also requires proportionally greater interference resolution to maintain behavioural performance. Likewise, a stimulus eliciting a

minimal interference detection signal would likely require only minimal levels of interference resolution.

One strategy for dissociating these two general processes would be to manipulate the availability of executive resources in a way that would differentially influence the extent of interference and the ability to resolve that interference. In the Sternberg task, changing the size of the memory load is a straight forward method for manipulating the availability of executive resources. In the case of increased memory load, the central executive capacity required to maintain the load would compete with demands for central executive processes supporting interference resolution. Thus, if the N450 is an index of active resolution of conflict, it should be markedly reduced under high load conditions. In contrast, under increased memory load, the amount of conflict experienced by the individual should not be reduced and may even be increased in response to interference-eliciting stimuli. Thus, if the N450 reflects a reactive response indexing the detection of interference, then reducing executive capacity will maintain or even increase the amount of interference associated with salient, non-target probes and *increase* the amplitude of the cortical responses reflecting detection (e.g., Donkers & van Boxtel, 2004). This dissociation would only be expected on correct trials when participants are attempting to meet the precise task goal (identify old versus new probes on the *current* trial).

Research on cognitive aging is at least suggestive of an interference resolution process underlying the N450. For instance, older adults produce smaller N450 amplitudes and demonstrate greater interference effects in Stroop tasks compared to younger adults (West, 2004; West et al., 2000; West & Schwarb, 2006). They also show

reduced interference-related activations in IFC during Sternberg interference tasks (Jonides et al., 2000). It would appear, therefore, that older adults exhibit a reduced efficiency in dealing with interference effects. Moreover, it is more parsimonious to suggest a break-down in a late-occurring corrective action that aids in the selection of appropriate responses than to suggest a decline in an interference detection process, especially in tasks where conflict is overt and salient (e.g., identifying ink colours during the Stroop task).

It is also possible that, because the Sternberg-elicited N450 appears to be generated by multiple frontal regions (ACC and IFC), there may be an interactive response across these regions (e.g., Fan et al., 2008). It may be that the relative activations of ACC and bilateral IFC are inversely related to response load. That is, one cortical generator may show greater interference detection signals, whereas another may show greater activation associated with an adaptive response, which would be reflective of interference resolution. In order to deal with this possibility, data were submitted to source analysis in order to separate differential patterns of activation in multiple brain areas contributing to the mean N450 response seen at the scalp.

Support for the model described above would depend on load manipulations reliably altering the size of the interference-related N450. It should also be noted, however, that the N450 in both Stroop and Sternberg tasks is a relatively subtle deflection additive to other co-occurring ERP components. In a previous study (Tays, Dywan, & Segalowitz, 2009; chapter 2 of this thesis), it was shown that proper stimulus controls are employed to reduce unintended effects of stimulus salience and familiarity. The N450 can also fail to show reliable differences from a neutral/non-interference

baseline due to it co-occurring with other ERP components elicited within a similar latency window, thus masking interference effects. For example, in the Sternberg paradigm, the P3b (Polich & Criado, 2006), also referred to as the parietal old/new effect (see Curran, 2004; Wilding, 2000) or late positive component (Segalowitz, Van Roon, & Dywan, 1997), typically occurs over parietal recording sites between 300 and 800 ms following stimulus presentation and can have the effect of producing a diffuse negativity (the negative dipole of the P3b activation) over frontal scalp sites. This frontal negativity can create a large and long lasting deflection that overlaps with the N450 and may also be sensitive to the proposed load manipulations.

The P3b and N450 are, nonetheless, clearly dissociable in function, have only partially overlapping topographies (and presumably different underlying neural generators), and a different time-course of activation so that using data reduction methods, specifically independent component analysis (ICA), could be used to isolate cortical activations to interference effects from other cortical signals (see Appendix 1 for a more in depth discussion of independent components analysis). Past research using ICA has successfully been able to isolate P3b activations during visual perception paradigms (Makeig et al., 1999), making it a reasonable assumption that the P3b and N450 can be disentangled in the current study. Therefore, after presenting a traditional analysis of mean cortical N450 amplitudes, segmented EEG data were decomposed using ICA and reconstituted to create ERP_{ICA} data reflecting the isolated $N450_{ICA}$ activations. These data will be otherwise processed and analyzed in identical fashion to the initial N450 data.

In summary, the present study was designed to investigate the nature of the N450 by varying the working memory (WM) load within the Sternberg task. This memory load manipulation involved varying the size of the target set that had to be retained in WM between two, four, and six items. A two-item load was expected to allow for near maximal executive resource availability and lead to very modest behavioural interference effects. A four item load was expected to produce behavioural interference effects similar to those observed in past research. A six-item load was expected to further increase behavioural interference effects beyond the four-item level because executive resources, needed to maintain the load, would not be available to resolve interference. If the N450 does indeed reflect an interference- or conflict-detection function, then increasing WM load should result in larger ERP component amplitudes. However, if the N450 is more reflective of the processes required to resolve proactive interference, then as load increases the ERP component amplitude should show a decrease in line with the decreasing availability of executive resources.

Method

Participants

Sixteen Brock University undergraduates (12 female; 18-24 years, $M = 20.4$, $SD = 1.4$) took part in the study and received research experience hours or a small honorarium for participating. All volunteers were right handed, had normal or corrected-to-normal vision, and were fluent in English. Exclusion criteria included neurological/psychiatric disorder, major medical conditions, or medications expected to affect neural function. The project received clearance from Brock University's Research Ethics Board and all participants gave informed consent.

Stimuli and Experimental Design

Participants were comfortably seated in a dimly lit, acoustically and electrically shielded testing room. They completed a variable load, delay-to-match Sternberg task, adapted from Tays et al. (2008; 2009) that created proactive interference by strategically presenting probe items from previous trials (see figure 4.1a). Stimuli consisted of common three and four letter words drawn from the MRC Psycholinguistic Database (www.psy.uwa.edu.au/mrcdatabase/uwa_mrc.htm) and presented in white font with a teal background on a 17-inch CRT monitor using E-Prime (Psychological Software Tools, 2004). All words were presented in lowercase and subtended a visual angle of 2.3 degrees at a distance of 50 cm. At the beginning of each trial, an empty, vertical rectangle appeared centered around the middle of the screen for 500 ms. Next, either two words (low WM load), four words (medium WM load) or six words (high WM load) were presented within the rectangle. Word stimuli appeared serially, starting at the top of the rectangle, at a rate of one word per second and remained visible until presentation of the final word. Participants were instructed to silently read and retain these words in memory. The retention interval varied pseudorandomly as 2800, 3000, 3200, 3400 or 3600 ms and was followed by a probe word appearing at the centre of the screen for 1500 ms. Participants responded by pressing buttons labelled “match” and “no match” with their left or right index finger (counterbalanced across participants). An inter-trial interval of 1500 ms preceded the next memory set. Trials were organized by load and presented in runs of 18 trials at a time in a pseudorandomized order (i.e., 18 low load trials, followed by 18 medium load trials, and then 18 high load trials). Ten of these 18-trial runs constituted one block of trials and a total of four blocks were

completed, each separated by a short break. The same pool of approximately 1000 words were used to create each block, but any single word served as a critical probe item in one block only and appeared as filler items in the other three blocks.

The probe matched an item in the target set on 50% of trials (match probe) and the remaining 50% of trials required a “no match” response and were divided into three conditions: neutral (or negative) probes, familiar probes, and response conflict probes. Neutral probes did not match any items in the current memory set and were not seen at any other point during the current block. As illustrated in figure 4.1b, familiarity-based and response-based interference manipulations were produced by strategically repeating non-target probes in previous trials. The non-matching probe of the familiar condition is seen as a memory set item on trials “ $n - 1$ ”. Any errors or increase in response time for familiar probe trials versus the neutral probes would reflect the added difficulty of overcoming proactive interference from previous trials. During the response conflict condition, the probe was a non-target that had just been presented as a positive probe on trial “ $n - 1$ ”, creating an additional response prepotency additive to familiarity-based interference.

The entire task consisted of 720 trials: 360 positive trials and 120 trials for each of the three non-target conditions. These were further divided equally across three memory loads for a total of 120 positive trials and 40 of each of the non-target trials per experimental condition. Each recording session began with twelve practice trials that included trials with each load size and interference manipulation. The task took approximately 80 minutes to complete.

Electrophysiological Recordings and Statistical Analysis

Electroencephalogram data were recorded using a 128-channel Hydrocel Sensor Net (Electrical Geodesics, Eugene, OR) sampled at 500 Hz with a 0.1–100 Hz band-pass filter and vertex reference. Impedance of all channels was kept below 50 k Ω . Data were processed off-line with a 1 Hz high-pass and 30-Hz low-pass filter and segmented into 1200-ms epochs (-200 to 0 ms baseline). Individual epochs were screened for noncephalic artifacts.^{4,1} Moderate eye artifacts were corrected using a program created in MATLAB studio (MathWorks, 2006) that removes the shared variance between bipolar eye channels and scalp electrodes. Epochs that remained were converted to an averaged ERP, with an average reference, baseline corrected (-200 to 0 ms), and then combined to create group averages.

All statistical analyses were corrected for violations of Mauchley's Test of Sphericity, where necessary, utilizing the Huynh-Feldt correction for estimating the F-Statistics; however, degrees of freedom are not adjusted in the text. Mean RTs are based on correct trials only and trimmed of responses that occurred more than 3 standard deviations from individual subject means. A Bonferroni correction was used to determine significance levels for multiple comparisons following analyses of collapsed means (when exploring main effects) and simple effects (when exploring interactions).

Independent Component Analysis

Segmented, single-trial data for all conditions were submitted to an independent component analysis following offline processing (i.e., artefact detection, 1-30 Hz filtering, eye-blink regression, and re-referencing). The 128 channels of the original data

were reduced to a 64 channel montage (See figure 4.2). No channels were included from the outermost row of the sensor net, around the ears and back of the head, because these channels frequently showed sporadic high levels of noise and small movement artefacts. Reducing the number of channels to 64 also reduced the computational burden of the analysis and maintained a high ratio between the number of data points used to create the ICA decomposition and the number of channels (64 channels as the input produced 64 ICA components in the output). We used the extended infomax algorithm with the natural gradient provided in EEGLab (Delorme & Makeig, 2004) to derive the independent components decomposition. The EEGLab algorithm can provide an improved decomposition of the EEG signal over the original infomax approach by Bell and Sejnowski (1995) because of its sensitivity to infrequently active signals (such as brief ERP components occurring once every several thousand time points). The algorithm used an asymptote in the learned weighting function (sensitivity level set to 10^{-7}) or a maximum of 512 iterations to identify the component structure. For a more in-depth description of ICA, see Appendix 1.

The first ICA decomposition was used to identify segments with unstable component signals (i.e., messy decompositions) and any small artefacts missed during the original raw data pruning. After these segments were removed, a second ICA decomposition was done and these components were used to isolate N450 activity. Independent components accounting for the N450 in each participant were identified using both timing and spatial weighting criteria: components must be maximally active between 300-600 ms following probe presentation and must project a topography that is negative over frontal sensors (the boundary sites to be considered frontal were E33, E28,

E29, E13, E6, E112, E111, E117, E116 & E122). Component selection was done manually but in blind fashion (i.e., the relative component activations for each condition and load were unknown during N450 component identification). These criteria led to the identification of between 2 and 5 components in each participant (mean = 3.4, SD = 0.9) that appeared to contribute to the N450. These specific independent components were back-projected to the scalp to recreate the segmented EEG_{ICA} data which was then averaged across condition for each individual and analysed in identical fashion as the original EEG data but referred to as the N450_{ICA} data.

Source Analysis Method

Source analysis was conducted in two steps. First we used the Low Resolution Electromagnetic Tomography algorithm (LORETA; Pascual-Marqui, Esslen, Kochi, & Lehmann, 2002) provided in GeoSource (Electrical Geodesics, Eugene, OR) to initially create likely brain electrical sources for the ICA-derived components. LORETA constrains source models using two criteria: First, source space is defined in a three-dimensional model (based on a reference brain built from the Talairach atlas of the Brain Imaging Centre of the Montreal Neurologic Institute) composed of 2,394 volume elements (voxels) each with a spatial resolution of 7 mm and preidentified as grey matter, white matter, or as within the hippocampus. Second, the source model is built on the assumption that brain activity modeled by adjacent voxels should show more synchronous activity than distant voxels. LORETA uses the weighted sum of electrical potentials from across the scalp to calculate current source densities for each voxel. This creates a “blurred-localized” image of the source model at every time point of the ERP

with the relative strength of activation for each voxel expressed in units scaled to amperes per square meter.

By using the LORETA algorithm to initially identify potential neural generators, we avoided the need to specify the initial number and possible locations of dipoles in the source model. However, in order to test the time course of the dipoles identified by LORETA, a secondary analysis was carried out using BESA (version 5.0, Megis Software, 2005). The four-shell ellipsoidal head model was used to fit generators to the 64 channel N450_{ICA} data based on the LORETA model. Minor adjustments to Talairach coordinates were made using the least-squares fitting procedure, minimizing the difference between measured and model-predicted waveforms, providing a precise location for dipole fits. This allowed for a secondary testing of the LORETA model fit as well as independent dipole activation profiles for each of the identified cortical sources during a 300 – 600 ms time window that should sufficiently capture activations associated with the N450.

Results

Behavioral Data

Accuracy. As expected, load and condition manipulations showed robust effects on mean error rates (see table 4.1). Error rates were analyzed in a 4 (condition) by 3 (load) repeated measures ANOVA. An interaction between condition and load, $F(6, 60) = 8.58, p < .001, \eta^2 = .36$, was followed up with analysis of the simple effect of condition for each level of load. At low load (2 items), there was an effect of condition, $F(3, 45) = 6.63, p < .01, \eta^2 = .31$, such that both positive, $t(15) = 5.01, p < .01$, and response conflict probes, $t(15) = 2.59, p < .05$, led to higher error rates than negative or familiar

probes.^{4.2} At medium load (4 items), there was again an effect of condition, $F(3, 45) = 5.42, p < .01, \eta^2 = .27$, with both the familiar, $t(15) = 5.10, p < .01$, and response conflict condition, $t(15) = 2.91, p < .05$, as well as the positive condition, $t(15) = 3.06, p < .01$, showing higher error rates than the neutral condition. At high load (6 items), there was also a robust effect of condition, $F(3, 45) = 20.76, p < .001, \eta^2 = .58$, such that both familiar, $t(15) = 6.98, p < .01$, and response conflict conditions, $t(15) = 6.16, p < .01$, as well as the positive condition, $t(15) = 8.07, p < .01$, showed higher error rates than the neutral condition.^{4.3}

Response times (RTs) were analyzed in a similar fashion (see table 4.2). The 4 (condition) by 3 (load) repeated measures ANOVA revealed an effect of condition, $F(3, 90) = 25.45, p < .001, \eta^2 = .63$, and load, $F(3, 90) = 29.03, p < .001, \eta^2 = .66$, but no interaction ($F < 1.5$). The load effect was seen as a significant increase in overall RT from low load (545 ms) to both medium (645 ms), $t(15) = 5.72, p < .001$ and high load (674 ms), $t(15) = 7.09, p < .001$, but only a trend in the increase from medium load to high load, $t(15) = 1.91, p = .075$. This effect represents the costs associated with maintaining the increased WM load and the incremental increase in time required to make serial comparisons between the probe and the items held in WM (Sternberg, 1966). The condition effect was seen as a significant increase in RT from neutral (588 ms) probes to the familiar (654 ms), $t(15) = 5.61, p < .001$, and response conflict probes (668 ms), $t(15) = 10.18, p < .001$, reflecting the difficulty overcoming the proactive interference from previously seen stimuli. Thus, considering these behavioural effects together, it appeared that the manipulations effectively increased the amount of interference (as indicated by both error rate and RTs) in the expected direction.

Electrophysiological Data

Visual inspection of the ERP waveforms showed an N450-like negativity of varying strength and topography at each of the three WM loads. Surveying the topographies, the two proactive interference conditions, relative to neutral, showed a modest but consistent numerically stronger N450 peak in the response conflict condition compared to the familiar condition. There was also a high degree of overlap in the topographies of the two proactive interference conditions, replicating past findings using this paradigm (Tays et al., 2008; 2009). With the high degree of consistency between cortical responses to the two types of interference, and for the sake of parsimony, the data presented here used a collapsed measure of these two conditions to form a single condition we will refer to as the proactive interference (PI) condition. The grand-averaged waveforms associated with the positive, neutral and collapsed proactive interference conditions at each load are shown in figure 4.3(a-c).

Evident as well is a clear P3b of varying strength over parietal sensors at each of the three WM loads. As usual, the P3b component appeared to project a negative (di)pole seen at frontal recording sites. In examining the grand-average topographies, it was clear that the P3b was contributing to frontal negativities because the amplitude of positive and negative ends of its dipole became active (at approximately 300 ms) and resolved within the same time course (at approximately 700 ms).

N450. Frontal negativities consistent with the N450 component observed in past research were observed over lateral and midline frontal sites. While there appeared to be a modest midline N450 effect (PI versus neutral) at each memory load, there also appeared to be load sensitive effects at frontal lateral sensors. To capture these laterality

effects, the N450 was measured as the average negativity between 400 and 475 ms following the probe at sites approximating midline Fz, left frontal F5 and right frontal F6. These data were submitted to a 3 (load) by 3 (condition) by 3 (site) repeated measures ANOVA that revealed a three way interaction between load, condition, and site, $F(8, 120) = 8.27, p < .01, \eta^2 = .36$, superseding main effects and lower-order interactions. To simplify interpretation of the interference effect the contrasts between the neutral and PI condition are presented in table 4.3 at each load and site.

The N450 for the PI condition showed an effect that was dependent on both load and sensor site. At low WM load, the PI condition produced a robust N450 effect at left frontal site, and a marginal effect at the central site. There was no interference effect at the right frontal site for the low load. At medium WM load there was no clear N450 effect at the left, central, or right frontal sites. This was surprising as N450 effects were found at fronto-central sites at this load level in two previous studies (Tays 2008; 2009). At the highest WM load there was no N450 for the PI condition at the left frontal site, but the neutral and PI conditions did differ at the central and right frontal sites. Taking these data together, the effect of load and condition appears to be dependent on the site of analysis. At low load, the most robust N450 effect was at left frontal sites. This effect appears to be diminished at the medium WM load and then entirely absent at the high load. In contrast, right frontal sensors showed the strongest interference-related negativity during high load trials with progressive reductions in amplitude in the medium and low conditions. This inverse pattern across frontal sites is suggestive of the presence of two frontal negativities in the time frame of the N450: one maximal at low load and the other maximal at high load. The large negativities seen for the positive

condition, frequently even larger than that of PI condition, appears to reflect the negative (di)pole of the P3b response and presents a confound for its analysis in the N450 time window. Moreover, the PI and neutral condition also produce sizeable P3b effects that could also be influencing the N450 effects reported above. First, an analysis of the P3b effect should be made to gauge if amplitude differences at parietal sites have a pattern of results that would confound interpretation of the N450 effects.

P3b. The P3b was measured at its peak, Pz, as the average amplitude between 300 and 500 msec following the probe. The overall deflection appeared to last considerably longer than this time window, but any effect of condition appears to be restricted to this first half of the positivity. P3b data were submitted to a 3 (condition: positive, neutral, and PI) by 3 (load: low, medium, and high) repeated measure ANOVA. There was a significant condition by load interaction, $F(4, 60) = 15.41, p < .001, \eta^2 = .51$, that superseded main effects. Simple effects analysis of the P3b at each WM load revealed an effect of condition at low load, $F(2, 30) = 66.37, p < .001, \eta^2 = .82$, that was caused by a larger P3b response to positive probes relative to neutral probes, $t(15) = 6.68, p < .001$, with no difference between PI and neutral, $t(15) = 1.44, ns$. There was a similar effect of condition at medium load, $F(2, 30) = 37.77, p < .001, \eta^2 = .72$, and once again the positive probe produced a stronger P3b than the neutral probe, $t(15) = 4.95, p < .001$, and the PI probes showed no difference relative to neutral, $t(15) = 0.96, ns$. The high load also produced an effect of condition, $F(2, 30) = 23.66, p < .001, \eta^2 = .61$, but in this case both the positive probe, $t(15) = 4.18, p < .01$, and PI probe, $t(15) = 2.84, p < .05$, showed a significant increase in P3b amplitude over neutral probes. Thus, the P3b is considered here to reflect the increased allocation of attention toward goal-relevant or

salient stimuli, being sensitive to old versus new probes at all levels of WM load. As the PI condition produces a significant P3b effect at the highest WM load, we were concerned that this effect may be contributing to the N450 responses at the fronto-central and right frontal site at high load. The only way to accurately measure the N450 response itself, therefore, would be if the effect of the P3b could be carefully partialled out. For this reason, we conducted a second analysis of N450 effects on ICA derived data (EEG_{ICA}), with the effect of the P3b removed, in an attempt to better isolate the effects of the proactive interference manipulations on frontal negativities ($N450_{ICA}$).

N450_{ICA}. The reconstituted ERP data containing only the components associated with N450 activation identified in the ICA^{4.4} were analyzed in identical fashion to the traditional ERP analysis presented above: measurements were taken as the average amplitude at right frontal F6, midline Fz, and left frontal F5 (see figure 4.4). Although the positive condition was not included in this analysis, it is included in the figure to display the dramatic reduction of the P3b response at Pz and the absence of the negativities for this condition at frontal sites seen in the original waveforms (Figure 4.3). The same time-window from 400-475 ms after the probe was used to collect average amplitudes, but it is interesting to note that the peak negativity at left frontal F5 occurred at approximately 460 ms, whereas the peak right frontal negativity at F6 occurred at approximately 410 ms. If the same cortical sources were producing these two frontal negativities, then the activation at the high working memory load should be delayed relative to the low load, but the opposite pattern was observed in the present data. Although amplitudes for $N450_{ICA}$ waveforms were considerably smaller than in the traditional analysis (i.e., $N450_{ICA}$ amplitudes were approximately half the size of the

traditional N450) there did appear to be robust PI effects showing the same lateralized pattern as that just previously described. Once again, a 3 (load) by 3 (condition) by 3 (site) repeated measures ANOVA revealed a three way interaction between load, condition, and site, $F(8, 120) = 15.65, p < .001, \eta^2 = .51$, superseding main effects and lower-order interactions. This interaction was followed up once again with contrasts for both the PI conditions relative to the neutral condition at each WM load and site (see table 4.4).

As evident in figure 4.4, across all WM loads, there was a clear N450_{ICA} PI effect at midline Fz, although the effect was significant only at medium and high loads. The left frontal (F5) N450_{ICA} was strongest at the low WM load, decreased at the medium load, and disappeared entirely at the high load. The reverse pattern was observed at the right frontal site (F6) with no effect at low load, a trend towards an N450_{ICA} effect at medium load, and the strongest effect at high load. Although not predicted, it appears from these data that there are at least two dissociable negativities underlying the canonical N450 effect observed in past research: one negativity appears at left frontal sites and is seen to decrease as WM load and behavioural interference effects increase, while the other appears at right frontal sites, is minimal at low load, and increases as load and behavioral interference effects increase. In order to ensure that these two negativities were not separately driven by inclusion of both the familiar and response conflict condition in the average PI measure (with one condition generating the right frontal effect and the other condition producing the left frontal effect), paired samples t-tests were conducted to the two PI conditions. Average amplitudes were measured from 400-475 ms after the probe at each load and condition at the peak sites of activation (F5,

F6, and Fz). Amplitude comparisons revealed no differences between the individual N450_{ICA} amplitudes produced for familiar versus response condition conditions at each load (all p -values > .35). The degree of similarity between the PI effects produced from the familiar and response conflict conditions (removing the negative condition) are shown in figure 4.5.

Source Analysis

The ERP analysis of cortical response to PI both before and after the ICA showed an interaction effect between condition, site and load that suggests two dissociable negativities underlying the typical N450 response. The next step was to investigate the underlying source models for the N450_{ICA}, and whether the lateralized frontal negativities found in the present study would map onto the three dipole model from a previous investigation (Tays et al., 2008). The N450_{ICA} effect was analyzed by making difference waves between PI and neutral condition grand averages. These data were used to create source models using the LORETA algorithm, included in the GeoSource statistics package, to test whether the neural generators of the lateralized scalp negativities could be localized to left and right frontal cortex. We analyzed the activity from 400 to 475 ms after the probe for the high and low WM conditions because they showed the strongest dissociation between right frontal and left frontal activations, with less distinct activations at the medium load.

The activation models for the LORETA source analysis are shown in figure 4.6. At low load, when the left frontal negativity was most active, there were robust activations in medial frontal ACC (BA 32) and anterior, inferior frontal voxels (BA 45/47). At the highest WM load, when the right frontal negativity was strongest, ACC

voxels again showed robust activation along with right anterior frontal cortex (BA 46/9). This model was corroborated by a secondary analysis of source activation in BESA, but with an additional investigation of the time-course of N450_{ICA} dipole activations. Adjustments for maximizing the BESA source model's fit (in the interval 400 to 475 ms) did have the effect of pulling the two lateral dipoles into slightly deeper positions (i.e., closer to the centre of the head), and may reflect differences in regularization between the BESA and LORETA algorithms (Grech et al., 2008). The BESA dipole models, with associated Talairach coordinates are shown in figure 4.7. This single model provided a good fit to the N450_{ICA} data across the three loads, accounting for a large proportion of the variance in the scalp waveforms (low load = 92%, medium load = 94%, high load = 89%). The overall activation pattern of the BESA dipoles were generally consistent with the LORETA model. Although the right frontal dipole in BESA showed some activation even at the low working memory load, it is clear that the left frontal activations decreased with increasing working memory load, while the right frontal dipole showed the opposite effect. Interestingly, the right frontal dipole activation appeared to be active prior to 400 ms, while the left frontal dipole activation reached its peaks during the around 460 ms. Also, activation of the right frontal dipole also appeared to be delayed in the high load, relative to low load. This delay may reflect the longer period of time required for memory scanning as the WM load increases. Although these observations are qualitative in nature, they can be useful in creating testable models of frontal lobe function in future research.

Together, these data are consistent with the view that at least two separate cortical networks underlie the typical N450. One in left frontal cortex that is operant when

executive resources are available and participants have little trouble overcoming PI manipulations and the other in right frontal cortex that is operant when executive resources are limited and interference effects present a greater challenge. It appears also that anterior cingulate cortex shows robust activation during PI conditions, but this area does not appear to be sensitive to the availability of executive resources.

Discussion

Understanding cognitive control requires greater specification of the mechanisms underlying the reliably observed patterns of brain activation associated with conflict/interference effects. The under-specification of mechanisms underlying cortical activation, as seen in the use of vague terms such as *conflict processing*, limits the usefulness with which empirical findings might move along theoretical debate. Research on the interference related N450 has yet to produce clear evidence pointing to a specific information processing function. Speculations could be made that this frontally-generated negativity is the manifestation of any of a variety of cognitive control functions, such as the detection of response conflict (e.g., Botvinick et al., 2001; Swick & Turken, 2002), the refreshing of stimulus or task context representations in WM (e.g., Derrfuss et al., 2004), the allocation of attention (e.g., Weissman, Gopalakrishnan, Hazlett, & Woldorff, 2005), or the monitoring of current responses to determine whether they are in line with task goals (Ridderinkhof et al., 2004). However, in all cases where newly observed brain activations are linked to a particular cognitive process, it is necessary to devise an objective test of the validity of the model.

The current study was intended to test the validity of two possible models of the cognitive function underlying the interference-related N450, a component reliably

observed in various forms of the Stroop task (e.g., Jongen & Jonkman, 2010; Markela-Lerenc et al., 2004; Rebai et al., 1997; West et al., 2004) and Sternberg tasks with proactive interference manipulations (Du et al., 2008; Tays et al., 2008; Tays et al., 2009). Working memory load was manipulated by changing the size of the Sternberg memory set in order to dissociate resource dependent mechanisms from resource-independent mechanisms underlying the N450. If the N450 reflected the resolution of interference through the application of executive resources, then its amplitude should be maximal at low load and decline as executive resources are committed to maintain larger memory loads. However, if the N450 reflected an automatic response to some form of conflict in information processing, such as what would be expected from a simple conflict monitoring mechanism, then its amplitude should increase as interference effects increase from low to high load.

Behavioural results indicated that the load manipulation did increase interference effects, mostly seen as increases in error rates and RTs, providing a manipulation check that needed to be satisfied in order to properly test the hypotheses relating to the electrophysiological data. Inspection of grand average waveforms showed a strong P3b at parietal recording sites and what appeared to be N450 responses at frontal sites. A traditional ERP analysis revealed a robust P3b effect, such that larger positivities were seen in response to positive probes than to neutral (i.e., new) probes. Positive probes elicited larger P3b amplitudes than PI probes, but the PI probes also elicited larger P3b responses than the neutral probes at the highest WM load. This pattern of P3b response has also been observed for younger adults during dual-tasks and may reflect greater difficulty in aborting attention allocation to salient, non-targets (i.e., interference probes

during high working memory load). The negative (di)pole of the parietal P3b was observed as a large and long lasting negativity over frontal recording sites, overlapping with the measurement window of the N450. As a result of this effect, traditional measurement of average N450 amplitudes over frontal recording sites revealed significantly larger negativities for positive than neutral probes, an effect even larger than the frontal negativity elicited by PI probes. In order deal with the possible confound from the negative dipole of the P3b, an independent component analysis (ICA) was used to separate these overlapping activations. The reconstituted ERP was based solely on components showing topographies and time courses similar to the N450, thus removing the targetness or salience effect of the P3b but retaining the ERP interference effect (the remaining frontal negativity is referred to here as the N450_{ICA}).

Analysis of the N450_{ICA} revealed two dissociable patterns of activation organized by sensor location. At low load, there was a clear negative deflection at left frontal sites that remained at medium load but was greatly reduced by the high WM load. This activation was consistent with an interference resolution processes that would be strongest to PI probes at low load and weakest at high load, during which executive resources are committed to maintaining the WM set. A separate negativity appeared at right frontal recording sites that was weakest at low load and strongest at high load. This pattern of activation was in line with a reflexive/automatic response to the presence of interference that grew larger as interference effects increased.

N450_{ICA} data were submitted to a source analysis using LORETA that first localized activity specific to interference manipulations to anterior cingulate cortex (ACC), and two lateral frontal generators. The N450_{ICA} activation at right frontal sites

was localized to the right frontal generator (right frontal BA 46/9) and the N450_{ICA} at left frontal sites was localized to the left frontal generator (left frontal BA 45/47). A secondary source analysis using BESA corroborated the LORETA analysis and gave time course information for each dipole. Interestingly, the right frontal generator showed modest activation at the low memory load and this activation preceded the left frontal activity. However, the right frontal generator was maximal at high load, and this activation was delayed relative to the low load, as one might expect due to the increased size of the memory set and the required time to complete an exhaustive search of working memory items (Sternberg, 1966). The ACC generator produced moderate activation irrespective of memory load. Although the precise location of the lateral frontal ERPs may be difficult to specify with confidence, the use of ICA and source analysis in the present study makes for a compelling argument that the left and right frontal negativities are generated by separate cortical networks themselves supporting dissociable cognitive control functions.

A dual-mechanism model of automatic conflict-related responses that *are not* dependent on executive resources in right frontal cortex, and a left frontal mechanism that *is* dependent on executive resources is generally consistent with other research on the brain-basis of responses to internal states of cognitive interference. However, it should first be noted that a considerable body of research has supported models wherein anterior cingulate cortex acts as a very general mechanism for performance monitoring (making ongoing evaluations of the appropriateness of specific actions) while lateral frontal cortex exerts control (e.g., Mansouri, Tanaka, & Buckley, 2009; Ridderinkhof et al., 2004). In the present study, it was hypothesized that if there were multiple processes

underlying the N450, then one would likely be carried out by ACC and the other by lateral-frontal areas. However, the ACC generator did not show load sensitivity, speaking against a moderating effect of executive resources or the extent of the interference effect in the function it carries out. This is certainly not consistent with findings using other paradigms that do reveal ACC sensitivity to the extent of interference and response conflict (e.g., Mansouri et al., 2009; Nieuwenhuis, Yeung, van den Wildenberg, & Ridderinkhof, 2003; Yeung & Nieuwenhuis, 2009). It could at least be speculated that the ACC's lack of sensitivity to resource availability supports an interference detection role. However, considering that the contribution of the ACC may be difficult to accurately gauge, given the simultaneously marked changes in the two lateral generators, the current data do not speak strongly to the precise role of medial-frontal activations in the current task.

In contrast, the differential activation at right lateral and left lateral sensor sites speaks strongly to the presence of separate functions. There have been proposals that different frontal areas are specialized to deal with different forms of interference, such as right-frontal involvement in the control of conflict at the level of response selection versus left frontal involvement in non-response related interference (Milham et al., 2001). However, the present method produced data revealing a much stronger distinction in function with right frontal areas showing activation directly-related to the extent of interference (consistent with interference detection or a reflexive response control function not dependent on resource availability) while left frontal activations are dependent on resource-availability (consistent with an intentional application of top-down control to meet task requirements).

Attempts have also been made to specify how such functions would be carried out under a variety of task conditions. For instance, left frontal cortex may resolve interference by applying executive resources to refresh internal representations of task relevant information to overcome the effects of distracters (Brass et al., 2002; Derrfuss et al., 2005; Derrfuss et al., 2004) or amplification of task-relevant target features (Egner & Hirsch, 2005). Such a function would be expected to be most active at low load, because active refreshing of internal representations (whether specific items or task requirements) would require applying executive control resources. An impressive program of research by the investigators of the original fMRI study on which we originally based our Sternberg task (i.e., Nelson et al., 2003) has shown a consistent association between interference resolution within WM and activations in left inferior frontal gyrus, particularly when stimuli are verbal in nature (Jonides & Nee, 2006; Nelson et al., 2009).

The likely role of right frontal activation in cognitive control may be more difficult to determine considering that it could reflect either interference detection or some form of reflexive response control not heavily dependent on executive resources. However, multiple lines of research have supported an association between the regulation of motor response selection and right frontal cortex both from lesion studies (e.g., Aron et al., 2003) and from research using trans-magnetic stimulation to deactivate targeted brain areas (Chambers et al., 2006). In the present study, the cognitive control function reflected by right frontal activation may be a global stop-signal that aids in suppressing maladaptive prepotent response tendencies and allows for subsequent re-evaluation of potential responses (Aron & Verbruggen, 2008). To be clear, such a mechanism could

be seen as free of the resource limitations inherent in focused top-down control because *all* responses are interrupted, including any response preparation related to the correct behaviour. Therefore, under conditions of low resources and high interference, an adaptive behaviour would be to withhold responding until uncertainty can be resolved. Recent ERP and imaging research has also revealed that activation of a (mainly right-lateralized) inhibitory control network in frontal cortex can be activated outside of awareness (van Gaal, Lamme, Fahrenfort, & Ridderinkhof, 2010; van Gaal, Ridderinkhof, Scholte, & Lamme, 2010). Although such a function would markedly increase response time, as we observed in the interference trials at the highest WM load in the present study, this may be the best strategy to avoid executing incorrect behaviours. Interestingly, this model would still require an interference/uncertainty detection mechanism; a role that may be carried out by other cortical areas, such as the ACC as mentioned above. However, testing such a proposal will require further research.

In conclusion, the present data support a dissociation of functions between different areas of frontal cortex in supporting various aspects of cognitive control. It is evident that the canonical N450 response (Du et al., 2008; Jongen et al., 2010; Tays et al., 2008; Tays et al., 2009) reflects a combination of control processes working in tandem to produce task-appropriate responses. In the present discussion, these cognitive control processes have been treated as unique functions, but it is well known that cortical areas outside of the frontal lobe (see Mansouri et al., 2009) and subcortical structures (e.g., Li, Yan, Sinha, & Lee, 2008) are also important for implementing cognitive control. Furthermore, while functional dissociations can be made between left

and right lateral frontal cortex, these dissociations are not absolute. For instance, response inhibition has also been shown to be supported by left inferior frontal cortex under certain circumstances (Swick et al., 2002). A focus of future research will be to understand the factors mediating the recruitment of one control function over another and how they might work together to overcome interference (Egner et al., 2007). The present study contributes to this line of research by identifying how multiple cognitive control functions underlying the interference-related N450 response contribute to the effective regulation of behaviour over changing levels interference and the availability of executive resources.

Chapter 5

General Discussion

Past research has consistently shown that a fronto-central negativity (the N450) is produced when healthy young adults are confronted with interference-eliciting stimuli, such as an incongruent stimulus in variants of the Stroop task (Jongen et al., 2010; Liotti, Woldorff, Perez, & Mayberg, 2000; Markela-Lerenc et al., 2004; West et al., 2004) or previously seen negative probes in variants of the Sternberg task (Du et al., 2008; Tays et al., 2008; Tays et al., 2009). It would appear that the N450 is associated with situations requiring a high level of cognitive control. Source analysis of its neural generators implicates both medial and lateral frontal structures (Markela-Lerenc et al., 2004; Tays et al., 2008; West et al., 2004), which are generally considered the seat of high-level cognitive control functions (Badre & Wagner, 2005; Bartholow et al., 2005; Brass & von Cramon, 2002; Bunge et al., 2001; Egner et al., 2005; Fuster 2000; Kerns et al., 2004; Miller 2000; Ridderinkhof et al., 2004; Rushworth, Walton, Kennerley, & Bannerman, 2004).

Older adults tend to show reductions in the ability to withstand interference effects, particularly as overall task difficulty increases (Czernochowski, Nessler, & Friedman, 2010; Schneider-Garces et al., 2010), and reductions in the magnitude of cortical responses associated with interference (e.g., Jonides et al., 2000; West 2000) dovetail with findings of detectable declines in frontal lobe integrity (Raz 1999; West 1996). Moreover, older adults produce unique cortical activation not seen in younger adults, such as a diffuse positivity over frontal sites referred to here as the frontal positivity (Tays et al. 2008). Similar unique brain activations in older adults have, in some studies, been shown to represent attempts to compensate for age-associated

decline in cognitive function (Cabeza et al., 2002; Davis et al., 2008; Gutchess et al., 2005). In contrast, other lines of research have identified unique areas of activation to be associated with cognitive decline (Colcombe et al., 2005; Logan et al., 2002). Thus, although the frontal positivity was predictive of poor performance in a previous study using the Sternberg task (Tays et al., 2008), the factors contributing to this relationship were unclear. The studies presented here were designed to advance understanding of both the interference-related N450 produced by younger adults and the frontal positivity observed in older adults.

Study 1 (Chapter 2). The initial study conducted for the dissertation was designed to address a methodological issue associated with the interference-inducing Sternberg task. Previous studies using this task employed a small stimulus set (i.e., lower case letters) that required extensive repetition of stimuli in addition to the manipulation-specific repetition intended to create familiarity-based and response-based proactive interference (e.g., Jonides, Smith, Marshuetz, Koeppel, & Reuter-Lorenz, 1998; Nelson et al., 2003; Tays et al., 2008). The study presented here tested the effects of general stimulus repetition by contrasting two Sternberg tasks that differed only in the size of their stimulus sets: In one task, a set of 20 common words were used, requiring extensive resampling, whereas the other task used a set of approximately 700 words that did not require any resampling of previously seen stimuli. It was hypothesized that extensive general repetition required by a small stimulus set would produce unintended interference effects, competing with the specific interference effects produced from planned task manipulations.

Results were in line with this hypothesis and probe-locked ERPs revealed that constant reuse of items from a small stimulus set introduces a long-lasting frontal negativity into the baseline condition of the Sternberg task. This negativity was produced during the time window of the interference-related N450 and resulted in an apparent attenuation of the N450 in response to familiarity-based proactive interference manipulations, an attenuation not seen in the task employing a large stimulus set. The moderating effect of constant stimulus repetition on the N450 was not surprising considering that the small set-size task created familiarity-based interference by presenting a current probe on trial $n-1$ (or both $n-1$ and $n-2$). These interference trials were, in turn, compared to “non-familiar” baseline probes, which may have appeared as recently as trial $n-4$. In sum, although common stimuli such as words, letters, numbers or everyday objects can not be entirely stripped of their familiarity, those using research designs targeting proactive interference effects should limit unintended interference effects to the extent possible by avoiding the general stimulus repetition required by small stimulus sets.

It should also be noted that this initial study served as a precursor to the latter two investigations. When further examining the frontal positivity (i.e., Chapter 3), a large stimulus set was used to avoid repetition-driven nonspecific interference so that familiarity could be an unambiguous indicator of probe identity (i.e., old or new). Our hypothesis, discussed in more detail in the next section, was that removal of all interference effects would result in the frontal positivity predicting improved memory performance in older adults. Although this hypothesis proved incorrect, the use of a large stimulus set avoided nonspecific interference effects and ensured a fair test of the

hypothesis. Also, in designing the study to further investigate the functional basis of the N450 (i.e., Chapter 4), isolating the underlying mechanisms for of the N450 required a careful isolation of interference effects. Allowing the presence of interference effects on cortical responses in the baseline condition, due to general item repetition, may have undercut the effect of intended interference manipulations. In fact, it is unclear whether independent components analysis could have separated intended interference manipulations from non-specific interference effects considering that they appear to elicit activation in a similar frontal network supporting cognitive control (Postle, Brush, & Nick, 2004). Employing a large stimulus set in the Sternberg tasks used in each of the two follow-up studies avoided these potential problems.

Study 2 (Chapter 3). This investigation was focused on the frontal positivity produced by older adults, previously shown to be insensitive to probe identity in the Sternberg task (i.e., old versus new), but with the overall mean amplitude of the component predicting modest impairment in working memory performance (Tays et al., 2008). Of primary interest in this follow-up study was whether the frontal positivity would show a positive relationship with behaviour that was consistent with a compensatory framework (e.g., Cabeza et al., 2002; Reuter-Lorenz & Lustig, 2005). Compensatory effects would be expected to occur under conditions that do not place high demands on cognitive control (e.g., Cabeza et al., 2004), in contrast to tasks wherein older participants must overcome interference (e.g., Colcombe et al., 2005). However, although the simple Sternberg task used in Chapter 3 should have minimized interference effects, analyses once again indicated an inverse relationship between the amplitude of the frontal positivity and memory accuracy.

ERP recordings in young adults during the Sternberg task revealed a surprisingly early sensitivity to targets versus non-targets as seen in the early posterior negativity, an effect compatible with past research on early top-down adjustments altering posterior sensory processing (e.g., Bar et al., 2006). This early component was particularly interesting because it predicted memory accuracy and response times, a relationship restricted to younger adults. These findings provided further support for the perspective that younger adults are able to rely on early and relatively automatic target discrimination during simple memory judgments, whereas older adults must rely more on later, controlled processing (Alain et al., 2004; Jacoby et al., 2005; Tays et al., 2008).

The data presented in Chapter 3 provided a replication of the stimulus-locked frontal positivity effect from Tays et al. (2008) and, because zero-order correlations with temporally neighbouring components (e.g., P1 and N1) did not predict behaviour, it appeared that this component offers a unique measure of the modest declines in working memory experienced by many older adults. However, the current data did not provide evidence for the mechanism that may underlie the frontal positivity. The presence of the inverse relationship with behaviour is, in itself, not evidence that the frontal positivity reflects cortical activation that directly reduces the efficient cognitive functioning, such as inhibition failure (e.g., Gazzaley & D'Esposito, 2007; Lustig, May, & Hasher, 2001) or non-selective cortical recruitment (e.g., Park 2000). However, the fact that the frontal positivity shows a consistent event-related response to the memory probe suggests, at the very least, that this component does not reflect simple cortical noise (see Li 2005). Other research reporting conspicuous ERP responses unique to older adults supported the view that the frontal positivity reflects compensation failure rather than cognitive

decline. For instance, Wolk et al. (2009) describe a positivity observed over frontal recording sites between 800 and 1200 ms in older adults and suggest that it reflects supplemental attempts at long-term memory retrieval. These data were similar to ours in that an ERP component over frontal recording sites was associated with poor performance but may reflect an attempt to compensate for cognitive decline. Whereas a compensation failure explanation is theoretically tenable, further research will be necessary to determine whether this model applies to the frontal positivity.

A study by Grady et al. (2003) describes the conditions that may be required to reveal a positive correlation between the frontal positivity and memory accuracy in individuals with age-related cognitive decline. Their study used functional imaging to reveal brain responses unique to healthy older adults and patients with early stage Alzheimer's disease that were produced in prefrontal and temporal regions during episodic and semantic memory tasks. When collapsing across both healthy older adults and patients, higher levels of cortical activation in these areas was predictive of poor memory performance. However, when the same analysis was conducted in the Alzheimer's group only, the extent of unique activation was predictive of preserved long-term recall. This relationship likely emerged because all of the Alzheimer's patients had relatively similar levels of disease-related decline in brain function but varying levels of compensatory activations and accompanying improvements in memory performance. In contrast, healthy older adults were far less likely to have memory impairments than patients and were also less likely to require compensatory activation. As an analogy, a similar result would occur if one were to relate the use of a walking cane in a population of older adults. Older adults with mobility problems would show a

high rate of cane usage while older adults with intact mobility would show minimal cane usage. While canes effectively improve mobility, their use would actually correlate with poor mobility. However, if a sample of older adults with similar levels of mobility problems were investigated, those who were able to use canes would show better mobility than similar older adults who did not to use them. Similarly, when Alzheimers' patients are investigated, those producing compensatory activation show better memory performance relative to those unable to enlist these compensatory processes and, as a result, suffer from the full impact of disease-related decline.

In the older sample described in Chapter 3, the highest functioning older adults would be expected to show minimal age-related decline and may have minimal requirements for compensation, whereas poorer functioning older adults might show compensatory activation proportional to their decline in normative brain function. Even if compensatory activations are helping this latter group to some extent they are not expected to outperform high-functioning older adults whose performance and brain response are similar to those of younger controls. However, if a sample of older adults with similar levels of modest cognitive impairment could be identified, such as through pre-screening with neuropsychological tests, than compensatory activations may be the primary source of individual differences and the frontal positivity may then show a positive relationship with behaviour. However, as extensive neuropsychological pre-testing or structural imaging may not always be feasible, measurement of within-subject variance in unique, age-related brain activations via single-trial-analysis (e.g., Debener et al., 2006) may provide the most effective avenue for follow up investigations. Here, the extent of structural decline is constant within a given subject, while compensatory

activation may vary from trial-to-trial. Thus, trials showing the strongest unique activation may co-occur with correct memory decisions, supporting a compensatory function. Further research using this strategy may finally offer a strong, direct test of whether the frontal positivity reflects compensation or is a sign of decline.

The validity of the present interpretations for the early posterior negativity and frontal positivity findings will require validation and extension during future research. However, speculating on a possible integrated model of cognitive functioning during simple short-term recognition (i.e., Sternberg-like task demands), based on the current data and literature, may be a useful strategy going forward. This may be particularly helpful when formulating tests of the relative involvement of the factors I put forward to explain performance in the Sternberg task both between younger and older adults and individual differences within each respective age group.

When explaining age-related difference between healthy young adults and healthy older adults, the key factor I have focused on is the reliance on relatively early versus late processing on the part of younger and older adults, respectively. Observation of the early posterior negativity indicated that young adults are able to make initial, rapid identifications of stimulus identity within approximately 100 milliseconds. The surprisingly rapid timing of this effect may be mediated by the ability to hold the precise identity of a limited number of possible target items in working memory (e.g., Agam et al., 2009) as was the case in the simple Sternberg task, or be highly predictable based on task context (see Dambacher, Rolfs, Gollner, Kliegl, & Jacobs, 2009). Also, there must be an effective mechanism for the top-down modulation of stimulus processing (Bar et al., 2006). Individual differences in the ability to maintain a set of possible targets, or

variability in the top-down control mechanism could lead to the individual differences in the early posterior negativity effect observed within the younger group.

Older adults are more likely to be inefficient at making these early identifications. Age-related difficulties in making effective early recognition of a stimulus are likely determined by a host of factors. For example, age-related decreases in speed of processing (e.g., Salthouse 2000), possibility due to reduced integrity of white matter tracts conveying top-down signals from frontal to posterior, sensory areas (Gordon et al., 2008; Raz, Ghisletta, Rodrigue, Kennedy, & Lindenberger, 2010), could reduce the likelihood of biasing processing at critical stages of stimulus identification. Also, inefficiency in suppressing or inhibiting task-irrelevant processing of external information (Lustig et al., 2001) or internal mental states (Sambataro et al., 2010) could hamper older adults' ability to effectively direct processing in favour of task-relevant information.

I would suggest that the ability to maintain context information (Braver & Barch, 2002; West et al., 2006), i.e., the awareness of what information is relevant and task rules regulating appropriate responses to this information, is also an important factor in explaining variability in early target processing. Weak maintenance of context information, and the ability to create attentional sets required under cognitively demanding conditions (see Velanova, Lustig, Jacoby, & Buckner, 2007) may make early, and relatively automatic identifications of target stimuli more difficult and would require older participants to rely more heavily on later, more controlled processing to evaluate stimulus identity and select appropriate responses. One might even speculate that the frontal positivity could reflect controlled attempts to allocate attention, similar

to a P3a-like response (see Polich 2007Polich, 2007), which may aid in stimulus categorization or refreshing task context information required to make the stimulus categorization.

Whereas the ability to maintain context information is most often used to explain age-differences in performance, it may also explain some individual differences within each age group, in addition to the prime factors already mentioned above. For example the younger adults that did not show early target sensitivity may actually respond to the task in a manner more similar to high functioning older adults, and must rely more heavily on later, more controlled processing. Although younger adults from Tays et al. (2008) who showed target sensitivity in the initial target sensitivity P3a response required lesser ongoing processing indexed by the P3b responses, there was no such relationship in the current data. Thus if heavier reliance on late controlled processing in younger adults has a cortical indicator, it has yet to be identified.

Study 3(Chapter 4). This study was designed to investigate the mechanism(s) underlying the interference-related N450 response as revealed by varying working memory load in order to dissociate resource-dependent processes from resource-independent processes. As working memory load increased from two, to four, to six items, young adults showed increasing effects of interference on behavioural responses and a rather dramatic change in the topography of the N450. However, traditional measures of the N450 appeared to be confounded by the negative (di)pole of the LPC response; this effect was also observed in Chapter 2 as a slow-going negativity in both the baseline and interference conditions (even after controlling for general stimulus repetition). To ensure the N450 effect was not confounded by overlap with other ERP

components, an independent component analysis was conducted to isolate the interference effect. Both the traditional ERP analysis and the independent component analysis revealed that the N450 was observed over left frontal sensors at low load, when resources supporting cognitive control are maximal, and over right frontal sensors at high load, when resources are minimal. A source analysis showed that the scalp waveforms were compatible with distinct left (BA 45/47) and right (BA 46/9) frontal generators for the respective scalp topographies and a consistent degree of activation in the anterior cingulate cortex (BA 32) irrespective of load.

Integrating these results with current research on frontally-mediated cognitive control mechanisms suggests that the left frontal activation during the N450 may reflect the resolution of interference by applying executive resources to refresh internal representations of task relevant information to overcome the effects of distracters (Brass et al., 2002; Derrfuss et al., 2005; Derrfuss et al., 2004) or the amplification of specific task-relevant target features (Egner et al., 2005). It may also be that the left frontal N450 reflects a function specialized for interference resolution of verbal representations in working memory (Jonides et al., 2006; Nelson et al., 2009). A useful follow-up to the current project would be to investigate the effects of left frontal versus right frontal activations in response to non-verbal stimuli.

Whereas the right frontal activation could reflect conflict detection, this function may actually be carried out by the anterior cingulate cortex which showed robust activation in each interference condition and is consistently associated with monitoring functions (e.g., Carter & van Veen, 2007; Ridderinkhof et al., 2004), in addition to a proposed role in directly implementing cognitive control (e.g., Siltan et al., 2010). Right

frontal cortex activation has been associated with the regulation of motor response selection in lesion studies (e.g., Aron et al., 2003) and trans-magnetic stimulation (TMS) deactivation studies (e.g., Chambers et al., 2006). Moreover, a top-down, global stop function triggered by a combination of high levels of conflict and low levels of response certainty would be effective in situations where interference is high and correct responding is perceived as more important than fast responding (see Aron et al., 2008). Altering the emphasis placed on response speed and analyzing the cortical responses when participants respond incorrectly may offer further insight into the specific nature of the function supported by right frontal cortex.

The findings in Study 3 also shine a new light on the data from my Master's research (Tays et al., 2008). Although, as a group, the younger adults in that project produced a clear fronto-central N450, there was considerable variability in individual subject topographies. At the time, we noted the finding but made no attempt to explain it. In light of the present data, it may be that participants with larger working memory capacities may have shown more robust left frontal interference resolution response at relatively high loads in comparisons to participants with low working memory capacity (see Mecklinger, Weber, Gunter, & Engle, 2003). The older adults from my Master's project also showed a high degree of variability in their ERP responses, with many showing a combination of frontal positivity and weak lateralized N450-like components. These observations may reflect the fact that older adults appear to be more sensitive the degree of working memory load than younger adults. Recent research has shown that qualitative changes in cortical response appear when older adults hold approximately four items in working memory whereas younger adults show similar changes only when

approximately six items are maintained (Cappell, Gmeindl, & Reuter-Lorenz, 2010; Schneider-Garces et al., 2010). Thus, measuring individual differences and age-related difference in working memory capacity may be an important factor in further understanding the shift of activation from left frontal to right frontal cortical sources.

Although the cortical activation that underlies the N450 is reliably associated with task demands that require a high level of cognitive control, the mean component amplitudes between younger adults do not predict mean subject response times or error rates in my Master's data or data reported here. However, moving beyond measuring only mean levels of activation and performance can prove useful (e.g., Bellgrove, Hester, & Garavan, 2004). As was suggested with the frontal positivity, there may be at least as much variability in within-subject responses as between-subject responses and, therefore, single-trial activations in left and right frontal cortex may be shown to predict response latency and the likelihood of errors.

Interestingly, the addition of interference manipulations to simple memory recognition following short delays appears to nullify younger adults' ability to make very early, automatic stimulus identifications as evidenced by the lack of any apparent early posterior negativity in my Master's data or in the present studies (i.e., chapters 2 and 4). This was true even at the lowest working memory load tested in chapter 4, when only 2 items must be maintained in working memory and performance was minimally encumbered by interference. However, it is currently unclear whether this difference between the tasks reflects a strategy shift between simple recognition tasks and interference inducing tasks, or whether application of top-down control in preparation of

dealing with interference precludes applying resource to influence early stimulus processing.

Future Research

Although the three stand-alone studies presented here address separate questions, they were carried out with a larger plan in mind, i.e., to gain further understanding of how cognitive control functions are carried out by younger and older adults in their attempt to overcome interference in WM. However, first it was necessary to step back to investigate how basic working memory decisions are carried out without the need for high levels of cognitive control. Moreover, investigating how cognitive control functions are carried out in younger adults is a prerequisite to understanding the implications of aging effects on brain areas supporting adaptive responses to distraction and interference. Just as the present studies followed on the results of my initial Master's research, using the findings from the current investigations as the basis for further studies will hopefully advance my general line of enquiry on cognitive control processes in younger and older adults.

For example, the frontal positivity observed in older adults may be augmented under conditions that place different demands on working memory (such as was done in Study 3). Additionally, altering the nature of memory demands may also prove useful. For example, memorizing a small set of target items (eg., f j k m) and then making old/new judgments to an ongoing list of probe items (eg., n-k-b-a-c-m...) would involve similar recognition functions as the Sternberg task but with lesser demands on working memory updating (see Hester & Garavan, 2005). Varying the size of the memorized set

or the frequency that items in the memory set are changed may selectively influence the magnitude of the frontal positivity and memory performance.

Another approach would be to use independent component analysis to investigate whether older adults actually produce N450-like negativities during the interference-inducing Sternberg task that are simply not visible in a traditional analysis of their electrophysiological responses because of overlap with the frontal positivity. Recent research suggests that older adults must rely more on reactive control than proactive control to meet task demands (Czernochowski et al., 2010), so it may be expected that they would heavily engage right frontal cortex to deal with response uncertainty.

It would also be possible to further study younger adults' cognitive control abilities under a variety of task demands in order to better understand the functions indexed by activations in left frontal, right frontal and medial frontal cortex. It would be particularly useful to investigate how the interference processes indexed by the N450 generalize to different task demands and types of stimuli. For instance, is the left frontal N450 only active on tasks involving verbal stimuli? If the right frontal N450 is related to countermanding response execution, it may appear in a broader range of tasks than the left frontal effect. It would also be useful to investigate the conditions that allow younger adults to make the very early target discriminations indexed by the early posterior negativity in Chapter 2. Does this effect actually rely on participants being aware of the possible probe items, as would be the case in the Sternberg task? Would younger adults immediately abandon early identification attempts in tasks where familiarity is misleading? If so, is there a strategic balance wherein one might rely on early identification if familiarity was only very rarely misleading?

Perhaps of most practical importance, it will be necessary to validate the associations between particular cortical activity revealed by imaging and specific event-related potentials. Bringing to bear both the spatial resolution of imaging and the temporal resolution of EEG, such as may be possible with co-recordings (see Cappell et al., 2010; Herrmann & Debener, 2008; Lemieux et al., 2001) or at the very least by recording both measures on the same participants (e.g., Bledowski et al., 2006). This would be an important step in explaining the differences between findings. This may be particularly important in identifying whether the frontal positivity observed using ERP methods reflects a similar form of activation as compensatory fronto-cortical activations identified during functional imaging.

Footnotes

- 2.1 Four separate lists of 20 randomly selected words were constructed to minimize differences between words appearing in the small and large set size lists. These four small set size lists were counterbalanced across participants.
- 2.2 The varying interstimulus interval between the memory set and probe could create expectancy effects just prior to probe onset. The baseline was constructed at a point early enough to ensure these effects could not yet be operant.
- 2.3 Considerations in scoring the N450: One might wonder if using identical N450 time windows (400-500 ms after the probe) for both set size tasks is misleading. In the small set-size waveform in particular, it appears that the response conflict condition may produce its maximal effect at approximately 550 ms. While an alternate analyses at this later time (500-600 ms) in the small set-size data did indicate an enlarged N450 in the response conflict condition, the general pattern of results during multiple comparisons of mean differences was identical to the original analysis.
- 3.1 The reduced level of differentiation in the parietal P3b in the incidental memory task is not surprising considering the large proportion of correct guesses that are likely to be included in the ERP averages for both groups. Despite this guessing, we note that younger adults still showed reliable discriminations in their cortical responses (i.e., P3b) to old vs new items.
- 3.2 To ensure that this relationship is specific to the late frontal positivity and not just individual differences in overall EEG power, we related the average component activation from the early posterior negativity, as well as the P1, N1,

and P3b to Sternberg memory accuracy in older adults, but found no similar relationships (all p -values $> .30$).

- 4.1 The segments identified as too noisy to include in the independent component analysis were also excluded for normal ERP analysis so that identical segments were used in both analyses.
- 4.2 Finding a significant number of false negatives on positive probe trials is typical of this paradigm and likely reflects combination of failing to maintain the memory set and a conservative response strategy.
- 4.3 In contrast to past research (Tays et al., 2008, 2009), error rates in the response conflict condition were not greater than the familiar condition at medium load ($p = .58$). It is unclear why this effect did not replicate but it appeared that the error rate was much higher for familiar probes than was observed in previous research, whereas error rate was at the expected level for the response conflict probes.
- 4.4 The individual subject N450 effects were expected to be relatively intact from before and after the ICA. It was clear that the magnitude of the effects were reduced following the ICA, partly due to the removal of the P3b but also likely a result of some variance lost during component decomposition. We were interested in how well the N450 effect was preserved from before and after the ICA, so a Pearson correlation were conducted relating the overall average N450 PI before after the ICA. We found a significant positive correlation between N450 and N450_{ICA} data ($r = .70$, $p < .01$, $R^2 = .49$). As the P3b effect was removed in the EEG_{ICA} data, we expected that there should be no association between the original P3b data and an identical measurement done after the ICA,

and this was generally what was found ($r=.28$, n.s.). Together, these data suggest that a considerable proportion of variance is shared in N450 amplitudes before and after the ICA, whereas little of the variance associated with the P3b retained after this component was removed from the data.

Refereneces

- Agam, Y., Hyun, J. S., Danker, J. F., Zhou, F., Kahana, M. J., & Sekuler, R. (2009). Early neural signatures of visual short-term memory. *Neuroimage*, 44(2), 531-536.
- Alain, C., McDonald, K. L., Ostroff, J. M., & Schneider, B. (2004). Aging: a switch from automatic to controlled processing of sounds? *Psychology of Aging*, 19(1), 125-133.
- Allen, J. S., Bruss, J., Brown, C. K., & Damasio, H. (2005). Normal neuroanatomical variation due to age: the major lobes and a parcellation of the temporal region. *Neurobiology of Aging*, 26(9), 1245-1282.
- Allen, P. A., Smith, A. F., Lien, M. C., Kaut, K. P., & Canfield, A. (2009). A multistream model of visual word recognition. *Attention, Perception and Psychophysiology*, 71(2), 281-296.
- Alvarez, J. A. & Emory, E. (2006). Executive function and the frontal lobes: A meta-analytic review. *Neuropsychology Review*, 16, 17-42.
- Amiez, C., Joseph, J. P., & Procyk, E. (2006). Reward encoding in the monkey anterior cingulate cortex. *Cerebral Cortex*, 16, 1040-1055.
- Andrews-Hanna, J. R., Snyder, A. Z., Vincent, J. L., Lustig, C., Head, D., Raichle, M. E., et al. (2007). Disruption of large-scale brain systems in advanced aging. *Neuron*, 56(5), 924-935.
- Aron, A. R., Fletcher, P. C., Bullmore, E. T., Sahakian, B. J., & Robbins, T. W. (2003). Stop-signal inhibition disrupted by damage to right inferior frontal gyrus in humans. *Nature Neuroscience*, 6(2), 115-116.
- Aron, A. R., Robbins, T. W., & Poldrack, R. A. (2004). Inhibition and the right inferior frontal cortex. *Trends in Cognitive Science*, 8(4), 170-177.
- Aron, A. R., & Verbruggen, F. (2008). Stop the presses: dissociating a selective from a global mechanism for stopping. *Psychological Science*, 19(11), 1146-1153.
- Baddeley, A. (1992). Working memory. *Science*, 255(5044), 556-559.
- Baddeley, A. D. (2001). Is working memory still working? *American Psychoogistl*, 56(11), 851-864.
- Baddeley, A. D. (2003). Working memory: Looking back and looking forward. *Nature Reviews Neuroscience*, 4, 829-839.

- Baddeley, A. D. & Andrade, J. (2000). Working memory and the vividness of imagery. *Journal of Experimental Psychology: General*, 129, 2521-2542.
- Baddeley, A. D., Emslie, H., & Nimmo-Smith, I. (1992). The speed and capacity of language processing (SCOLP) test: Thames Valley Test Company, Bury St. Edmunds.
- Baddeley, A.D. & Hitch, G. (1974). Working memory. In G.A. Bower (Ed.), *The psychology of learning and motivation* (Vol. 8, pp. 47–89). New York: Academic Press.
- Baddeley, A. Lewis, V. & Vallar, G. (1984). Exploring the articulatory loop. *The Quarterly Journal of Experimental Psychology Section A*, 36, 233 – 252.
- Baddeley, A. D., Thompson, N. & Buchanan, M. (1975). Word length and the structure of short-term memory. *Journal of Verbal Learning and Verbal Behavior*, 14, 575-589.
- Badre, D., & Wagner, A. (2005). Frontal lobe mechanisms that resolve proactive interference. *Cerebral Cortex*, 15, 2003-2012.
- Badre, D., & Wagner, A. D. (2004). Selection, integration, and conflict monitoring; assessing the nature and generality of prefrontal cognitive control mechanisms. *Neuron*, 41(3), 473-487.
- Badzakova-Trajkov, G., Barnett, K. J., Waldie, K. E., & Kirk, I. J. (2009). An ERP investigation of the Stroop task: the role of the cingulate in attentional allocation and conflict resolution. *Brain Research*, 1253, 139-148.
- Ball, K., Berch, D. B., Helmers, K. F., Jobe, J. B., Leveck, M. D., Marsiske, M., et al. (2002). Effects of cognitive training interventions with older adults: a randomized controlled trial. *JAMA*, 288(18), 2271-2281.
- Band, G. P., Ridderinkhof, K. R., & Segalowitz, S. (2002). Explaining neurocognitive aging: is one factor enough? *Brain and Cognition*, 49(3), 259-267.
- Banich, M. T., Milham, M. P., Atchley, R. A., Cohen, N. J., Webb, A., Wszalek, T., et al. (2000). Prefrontal regions play a predominant role in imposing an attentional 'set': evidence from fMRI. *Brain Research*, 10(1-2), 1-9.
- Bar, M., Kassam, K. S., Ghuman, A. S., Boshyan, J., Schmid, A. M., Dale, A. M., et al. (2006). Top-down facilitation of visual recognition. *PNAS*, 103(2), 449-454.

- Bareceló, F., Suwazono, S. & Knight, R. (2000). Prefrontal modulation of visual processing in humans. *Nature Neuroscience*, 3, 399-403.
- Bartholow, B. D., Pearson, M. A., Dickter, C. L., Sher, K. J., Fabiani, M., & Gratton, G. (2005). Strategic control and medial frontal negativity: beyond errors and response conflict. *Psychophysiology*, 42(1), 33-42.
- Bell, A. J., & Sejnowski, T. J. (1995). An information-maximization approach to blind separation and blind deconvolution. *Neural Computation*, 7(6), 1129-1159.
- Bellgrove, M. A., Hester, R., & Garavan, H. (2004). The functional neuroanatomical correlates of response variability: evidence from a response inhibition task. *Neuropsychologia*, 42(14), 1910-1916.
- Bledowski, C., Cohen Kadosh, K., Wibrall, M., Rahm, B., Bittner, R. A., Hoechstetter, K., et al. (2006). Mental chronometry of working memory retrieval: a combined functional magnetic resonance imaging and event-related potentials approach. *Journal of Neuroscience*, 26(3), 821-829.
- Botvinick, M. M., Braver, T. S., Barch, D. M., Carter, C. S., & Cohen, J. D. (2001). Conflict monitoring and cognitive control. *Psychological Review*, 108(3), 624-652.
- Brass, M., Ullsperger, M., Knoesche, T. R., von Cramon, D. Y., & Phillips, N. A. (2005). Who comes first? The role of the prefrontal and parietal cortex in cognitive control. *Journal of Cognitive Neuroscience*, 17(9), 1367-1375.
- Brass, M., & von Cramon, D. Y. (2002). The role of the frontal cortex in task preparation. *Cerebral Cortex*, 12, 908-914.
- Braver, T. S., & Barch, D. M. (2002). A theory of cognitive control, aging cognition, and neuromodulation. *Neuroscience and Biobehavioral Reviews*, 26(7), 809-817.
- Braver, T. S., Barch, D. M., Keys, B. A., Carter, C. S., Cohen, J. D., & Kaye, J. A. (2001). Context Processing in Older Adults: Evidence for a Theory Relating Cognitive Control to Neurobiology in Healthy Aging. *Journal of Experimental Psychology: General*, 130, 746-763.
- Braver, T. S., Barch, D. M., Keys, B. A., Carter, C. S., Cohen, J. D., Kaye, J. A., et al. (2001). Context processing in older adults: evidence for a theory relating cognitive

- control to neurobiology in healthy aging. *Journal of Experimental Psychology*, 130(4), 746-763.
- Buckner, R. L. (2004). Memory and executive function in aging and AD: multiple factors that cause decline and reserve factors that compensate. *Neuron*, 44(1), 195-208.
- Bunge, S. A., Ochsner, K. N., Desmond, J. E., Glover, G. H., & Gabrieli, J. D. (2001). Prefrontal regions involved in keeping information in and out of mind. *Brain*, 124(Pt 10), 2074-2086.
- Burgess, P. W., & Shallice, T. (1997). The relationship between prospective and retrospective memory: Neuropsychological evidence. In M. A. Conway (Ed.), *Cognitive models of memory. Studies in cognition* (pp. 247-272). Cambridge: MIT Press.
- Cabeza, R., Anderson, N. D., Locantore, J. K., & McIntosh, A. R. (2002). Aging gracefully: compensatory brain activity in high-performing older adults. *Neuroimage*, 17(3), 1394-1402.
- Cabeza, R., Daselaar, S. M., Dolcos, F., Prince, S. E., Budde, M., & Nyberg, L. (2004). Task-independent and task-specific age effects on brain activity during working memory, visual attention and episodic retrieval. *Cerebral Cortex*, 14(4), 364-375.
- Cabeza, R., Grady, C. L., Nyberg, L., McIntosh, A. R., Tulving, E., Kapur, S., et al. (1997). Age-related differences in neural activity during memory encoding and retrieval: a positron emission tomography study. *Journal of Neuroscience*, 17(1), 391-400.
- Cappell, K. A., Gmeindl, L., & Reuter-Lorenz, P. A. (2010). Age differences in prefrontal recruitment during verbal working memory maintenance depend on memory load. *Cortex*, 46(4), 462-473.
- Cardillo, E. R., Aydelott, J., Matthews, P. M., & Devlin, J. T. (2004). Left inferior prefrontal cortex activity reflects inhibitory rather than facilitatory priming. *Journal of Cognitive Neuroscience*, 16(9), 1552-1561.
- Carter, C. S., & van Veen, V. (2007). Anterior cingulate cortex and conflict detection: an update of theory and data. *Cognitive, Affective, and Behavioral Neuroscience*, 7(4), 367-379.

- Chambers, C. D., Bellgrove, M. A., Stokes, M. G., Henderson, T. R., Garavan, H., Robertson, I. H., et al. (2006). Executive "brake failure" following deactivation of human frontal lobe. *Journal of Cognitive Neuroscience*, 18(3), 444-455.
- Chincotta, D., Underwood, G., Abd Ghani, K., Papadopoulou, E. & Wresinksi, M. (1999). Memory span for Arabic numerals and digit words: Evidence for a limited-capacity, visuo-spatial storage system. *Quarterly Journal of Experimental Psychology Section A*, 52, 325-351.
- Colcombe, S. J., Kramer, A. F., Erickson, K. I., & Scalf, P. (2005). The implications of cortical recruitment and brain morphology for individual differences in inhibitory function in aging humans. *Psychology of Aging*, 20(3), 363-375.
- Cohen, I. & Servan-Schreiber, D. (1992). Context, cortex and dopamine: A connectionist approach to behaviour and biology in schizophrenia. *Psychological Review*, 99,45-77.
- Conrad, R. & Hull, A. J. (1964). Information, acoustic confusion and memory span. *British Journal of Psychology*, 55, 429-432.
- Conway, A. R. A., & Engel, R. W. (1994). Working memory and retrieval: A resource-dependent inhibition model. *Journal of Experimental Psychology: General*, 123, 354-373.
- Corbetta, M., Miezin, F. M., Dobmeyer, S., Shulman, G. L., & Petersen, S. E. (1990). Attentional modulation of neural processing of shape, color, and velocity in humans. *Science*, 248(4962), 1556-1559.
- Corbetta, M., & Shulman, G. L. (2002). Control of goal-directed and stimulus-driven attention in the brain. *Nature Reviews Neuroscience*, 3(3), 201-215.
- Crottaz-Herbette, S., & Menon, V. (2006). Where and when the anterior cingulate cortex modulates attentional response: combined fMRI and ERP evidence. *Journal of Cognitive Neuroscience*, 18, 766-780.
- Curran, T. (2004). Effects of attention and confidence on the hypothesized ERP correlates of recollection and familiarity. *Neuropsychologia*, 42(8), 1088-1106.
- Czernochowski, D., Nessler, D., & Friedman, D. (2010). On why not to rush older adults--relying on reactive cognitive control can effectively reduce errors at the expense of slowed responses. *Psychophysiology*, 47(4), 637-646.

- Dambacher, M., Rolfs, M., Gollner, K., Kliegl, R., & Jacobs, A. M. (2009). Event-related potentials reveal rapid verification of predicted visual input. *PLoS One*, 4(3), e5047.
- Darowski, E. S., Helder, E., Zacks, R. T., Hasher, L., & Hambrick, D. Z. (2008). Age-related differences in cognition: The role of distraction control. *Neuropsychology*, 22, 638-644.
- Daselaar, S. M., Fleck, M. S., Dobbins, I. G., Madden, D. J., & Cabeza, R. (2006). Effects of healthy aging on hippocampal and rhinal memory functions: an event-related fMRI study. *Cerebral Cortex*, 16(12), 1771-1782.
- Davis, S. W., Dennis, N. A., Daselaar, S. M., Fleck, M. S., & Cabeza, R. (2008). Que PASA? The posterior-anterior shift in aging. *Cerebral Cortex*, 18(5), 1201-1209.
- Debener, S., Ullsperger, M., Siegel, M., & Engel, A. K. (2006). Single-trial EEG-fMRI reveals the dynamics of cognitive function. *Trends Cognitive Science*, 10(12), 558-563.
- Della Salla, S., Gray, C., Spinnler, H. & Trivelli, C. (1998). Frontal Lobe Functioning in Man: The Riddle Revisited. *Archives of Clinical Neuropsychology*, 13, 663-682.
- Delorme, A., & Makeig, S. (2004). EEGLAB: an open source toolbox for analysis of single-trial EEG dynamics including independent component analysis. *Journal of Neuroscience Methods*, 134(1), 9-21.
- Derrfuss, J., Brass, M., Neumann, J., & von Cramon, D. Y. (2005). Involvement of the inferior frontal junction in cognitive control: Meta-analyses of switching and Stroop studies. *Human Brain Mapping*, 25, 22-34.
- Derrfuss, J., Brass, M., & von Cramon, D. Y. (2004). Cognitive control in the posterior fronto-lateral cortex: evidence from common activations in task coordination, interference control and working memory. *NeuroImage*, 23, 604-612.
- D'Esposito, M., Cooney, J. W., Gazzaley, A., Gibbs, S. E. B., & Postle, B. R. (2006). Is the prefrontal cortex necessary for delay-task performance? Evidence from lesion and fMRI data. *Journal of the International Neuropsychological Society*, 12, 248-260.

- D'Esposito, M., Postle, B. R., Ballard, D., & Lease, J. (1999). Maintenance versus Manipulation of Information held in Working Memory: an Event-Related fMRI Study. *Brain & Cognition*, 41, 66-86.
- Devinsky, O., Morrell, M. J., & Vogt, B. A. (1995). Contributions of anterior cingulate cortex to behaviour. *Brain*, 118 (Pt 1), 279-306.
- Donkers, F. C., & van Boxtel, G. J. (2004). The N2 in go/no-go tasks reflects conflict monitoring not response inhibition. *Brain and Cognition*, 56(2), 165-176.
- Drewe, E. A. (1975). Go-no go learning after frontal lobe lesions in humans. *Cortex*, 11, 8-16.
- Du, Y., Xiao, Z., Song, Y., Wu, R., & Zhang, J. X. (2008). An electrophysiological signature for proactive interference resolution in working memory. *International Journal of Psychophysiology*, 69, 107-111.
- Dywan, J., Segalowitz, S., & Arsenault, A. (2002). Electrophysiological response during source memory decisions in older and younger adults. *Brain and Cognition*, 49(3), 322-340.
- Egner, T., Delano, M., & Hirsch, J. (2007). Separate conflict-specific cognitive control mechanisms in the human brain. *Neuroimage*, 35(2), 940-948.
- Egner, T., Etkin, A., Gale, S., & Hirsch, J. (2008). Dissociable neural systems resolve conflict from emotional versus nonemotional distracters. *Cerebral Cortex*, 18(6), 1475-1484.
- Egner, T., & Hirsch, J. (2005). Cognitive control mechanisms resolve conflict through cortical amplification of task-relevant information. *Nature Neuroscience*, 8(12), 1784-1790.
- Eichele, T., Calhoun, V. D., & Debener, S. (2009). Mining EEG-fMRI using independent component analysis. *International Journal of Psychophysiology*, 73(1), 53-61.
- Erixon-Lindroth, N., Farde, L., Wahlin, T. B., Sovago, J., Halldin, C., & Backman, L. (2005). The role of the striatal dopamine transporter in cognitive aging. *Psychiatry Research*, 138(1), 1-12.

- Fabiani, M., Friedman, D., & Cheng, J. C. (1998). Individual differences in P3 scalp distribution in older adults, and their relationship to frontal lobe function. *Psychophysiology*, 35(6), 698-708.
- Fair, D. A., Dosenbach, N. U., Church, J. A., Cohen, A. L., Brahmbhatt, S., Miezin, F. M., et al. (2007). Development of distinct control networks through segregation and integration. *PNAS*, 104(33), 13507-13512.
- Fan, J., Hof, P., Guise, K. G., Fossella, J. A., & Posner, M. I. (2008). The functional integration of the anterior cingulate cortex during conflict processing. *Cerebral Cortex*, 18, 796-805.
- Fellows, L. K., & Farah, M. J. (2005). Is anterior cingulate cortex necessary for cognitive control? *Brain*, 128(Pt 4), 788-796.
- Fenske, M. J., Aminoff, E., Gronau, N., & Bar, M. (2006). Top-down facilitation of visual object recognition: object-based and context-based contributions. *Brain Research*, 155, 3-21.
- Folstein, M. F., Folstein, S. E., & McHugh, P. R. (1975). "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *Journal of Psychiatric Research*, 12(3), 189-198.
- Fotenos, A. F., Snyder, A. Z., Girton, L. E., Morris, J. C., & Buckner, R. L. (2005). Normative estimates of cross-sectional and longitudinal brain volume decline in aging and AD. *Neurology*, 64(6), 1032-1039.
- Foxe, J. J., & Simpson, G. V. (2002). Flow of activation from V1 to frontal cortex in humans. A framework for defining "early" visual processing. *Experimental Brain Research*, 142(1), 139-150.
- Friedman, D. (2003). Cognition and aging: a highly selective overview of event-related potential (ERP) data. *Journal of Clinical and Experimental Neuropsychology*, 25(5), 702-720.
- Friston, K. J., Price, C. J., Fletcher, P., Moore, C., Frackowiak, R. S. J., & Dolan, R. J. (1996). The trouble with cognitive subtraction. *NeuroImage*, 4, 97-104.
- Fuster, J. M. (2000). Executive frontal functions. *Experimental Brain Research*, 133(1), 66-70.

- Fuster, J. M. (2002). Frontal lobe and cognitive development. *Journal of Neurocytoogy*, 31(3-5), 373-385.
- Gazzaley, A., Clapp, W., Kelley, J., McEvoy, K., Knight, R. T., & D'Esposito, M. (2008). Age-related top-down suppression deficit in the early stages of cortical visual memory processing. *PNAS*, 105(35), 13122-13126.
- Gazzeley, A., Cooney, J. W., Rissman, J., & D'Esposito, M. (2005). Top-down suppression deficit underlies working memory impairment in normal aging. *Nature Neuroscience*, 8, 1298-1300.
- Gazzaley, A., & D'Esposito, M. (2007). Top-down modulation and normal aging. *Annals of the New York Academy of Sciences*, 1097, 67-83.
- Gordon, B. A., Rykhlevskaia, E. I., Brumback, C. R., Lee, Y., Elavsky, S., Konopack, J. F., et al. (2008). Neuroanatomical correlates of aging, cardiopulmonary fitness level, and education. *Psychophysiology*, 45(5), 825-838.
- Grady, C. L., Maisog, J. M., Horwitz, B., Ungerleider, L. G., Mentis, M. J., Salerno, J. A., et al. (1994). Age-related changes in cortical blood flow activation during visual processing of faces and location. *Journal of Neuroscience*, 14(3 Pt 2), 1450-1462.
- Grady, C. L., McIntosh, A. R., Beig, S., Keightley, M. L., Burian, H., & Black, S. E. (2003). Evidence from functional neuroimaging of a compensatory prefrontal network in Alzheimer's disease. *Journal of Neuroscience*, 23(3), 986-993.
- Grech, R., Cassar, T., Muscat, J., Camilleri, K. P., Fabri, S. G., Zervakis, M., et al. (2008). Review on solving the inverse problem in EEG source analysis. *Journal of Neuroengineering and Rehabilitation*, 5, 25.
- Greenwood, P. M. (2000). The frontal aging hypothesis evaluated. *Journal of the International Neuropsychological Society*, 6(6), 705-726.
- Gutchess, A. H., Welsh, R. C., Hedden, T., Bangert, A., Minear, M., Liu, L. L., et al. (2005). Aging and the neural correlates of successful picture encoding: frontal activations compensate for decreased medial-temporal activity. *Journal of Cognitive Neuroscience*, 17(1), 84-96.

- Hanslmayr, S., Pastotter, B., Bauml, K. H., Gruber, S., Wimber, M., & Klimesch, W. (2008). The electrophysiological dynamics of interference during the Stroop task. *Journal of Cognitive Neuroscience*, 20(2), 215-225.
- Hasher, L., Quig, M. B., & May, C. P. (1997). Inhibitory control over no-longer-relevant information: adult age differences. *Memory and Cognition*, 25(3), 286-295.
- Hartley, A. A. (1992). Attention. In F.L.M. Craik & Salthouse (Eds.). *The handbook of aging and cognition* (3-49). Hillsdale, NJ: Erlbaum.
- Hazeltine, E., Poldrack, R. & Gavrieli, J.D.E. (2000). *Journal of Cognitive Neuroscience*, 12 (supp. 2), 118-29.
- Hebb, D.O. (1939). Intelligence in man after large removals of cerebral tissue: Report of four left frontal lobe cases. *The Journal of General Psychology*, 21, 73-87.
- Herauld, J., & Jutten. (1986). Space or time adaptive signal processing by neural network models. *American Institute of Physics Conference Proceedings*, 151, 206-211.
- Herrmann, C. S., & Debener, S. (2008). Simultaneous recording of EEG and BOLD responses: a historical perspective. *International Journal of Psychophysiology*, 67(3), 161-168.
- Hester, R., & Garavan, H. (2005). Working memory and executive function: the influence of content and load on the control of attention. *Memory and Cognition*, 33(2), 221-233.
- Heuninckx, S., Wenderoth, N., Debaere, F., Peeters, R., & Swinnen, S. P. (2005). Neural basis of aging: the penetration of cognition into action control. *Journal of Neuroscience*, 25(29), 6787-6796.
- Hillyard, S. A., & Mangun, G. R. (1987). Sensory gating as a physiological mechanism for visual selective attention. *Electroencephalography and Clinical Neurophysiology*, 40, 61-67.
- Hommel, B., Ridderinkhof, K. R., & Theeuwes, J. (2002). Cognitive control of attention and action: issues and trends. *Psychological Research*, 66(4), 215-219.
- Jacoby, L. L., Bishara, A. J., Hessels, S., & Toth, J. P. (2005). Aging, subjective experience, and cognitive control: dramatic false remembering by older adults. *Journal of Experimental Psychology*, 134(2), 131-148.

- Jacoby, L. L., Kelley, C. M., & McElree, B. D. (1999). The role of cognitive control: Early selection versus late correction. In S. Chaiken & Y. Trope (Eds.), *Dual-process theories in social psychology* (pp. 383-400). New York: Guilford Press.
- Jones, A. C., Cho, R. Y., Nystrom, L. E., Cohen, J. D., & Braver, T. S. (2002). A computational model of anterior cingulate function in speeded response tasks: Effects of frequency, sequence, and conflict. *Cognitive, Affective & Behavioral Neuroscience*, 2, 300-317.
- Jongen, E. M., & Jonkman, L. M. (2010). Effects of concurrent working memory load on distractor and conflict processing in a name-face Stroop task. *Psychophysiology*.
- Jonides, J., Marshuetz, C., Smith, E., Reuter-Lorenz, P. A., Koeppe, R. A., & Hartley, A. (2000). Age Differences in Behaviour and PET Activation Reveal Differences in Interference Resolution in Verbal Working Memory. *Journal of Cognitive Neuroscience*, 12, 188-196.
- Jonides, J., & Nee, D. E. (2006). Brain mechanisms of proactive interference in working memory. *Neuroscience*, 139(1), 181-193.
- Jonides, J., Smith, E. E., Marshuetz, C., & Koeppe, R. A. (1998). Inhibition in verbal working memory revealed by brain activation. *PNAS*, 95, 8410-8413.
- Kane, M. J., & Engle, R. W. (2002). The role of prefrontal cortex in working-memory capacity, executive attention, and general fluid intelligence: an individual-differences perspective. *Psychological Bulletin and Review*, 9(4), 637-671.
- Kane, M. J., Hasher, L., Stoltzfus, E. R., Zacks, R. T., & Connelly, S. L. (1994). Inhibitory attentional mechanisms and aging. *Psychology of Aging*, 9(1), 103-112.
- Kennerley, S. W., Walton, M. E., Behrens, T. E. J., Buckley, M. J., & Rushworth, M. F. S. (2006). Optimal decision making and the anterior cingulate cortex. *Nature Neuroscience*, 9, 940-947.
- Kerns, J. G., Cohen, J., MacDonald III, A. W., Cho, R. Y., Stenger, A. V., & Carter, C. S. (2004). Anterior Cingulate Conflict Monitoring and Adjustments in Control. *Science*, 303, 1023-1028.

- Knight, R. T., Scabini, D. & Woods, D. L. (1989). Prefrontal cortex gating of auditory transmission in humans. *Brain Research*, 18, 338-342.
- Knight, R. T., Staines, W. R., Swick, D. & Chao, L. L. (1999). Prefrontal cortex regulates inhibition and excitation in distributed neural networks. *Acta Psychologica*, 101, 159-178.
- Kok, A. (2000). Age-related changes in involuntary and voluntary attention as reflected in components of the event-related potential (ERP). *Biological Psychology*, 54(1-3), 107-143.
- Kok, A. (2001). On the utility of P3 amplitude as a measure of processing capacity. *Psychophysiology*, 38(3), 557-577.
- Konishi, S., Nakajima, K., Uchida, I., Kikyo, H., Kameyama, M., Miyashita, Y. (1999). Common inhibitory mechanism in human inferior prefrontal cortex revealed by event-related fMRI. *Brain*, 122, 981-991.
- Kramer, A. F., Erickson, K. I., & Colcombe, S. J. (2006). Exercise, cognition, and the aging brain. *Journal of Applied Physiology*, 101(4), 1237-1242.
- Kveraga, K., Boshyan, J., & Bar, M. (2007). Magnocellular projections as the trigger of top-down facilitation in recognition. *Journal of Neuroscience*, 27(48), 13232-13240.
- Langenecker, S. A., & Nielson, K. A. (2003). Frontal recruitment during response inhibition in older adults replicated with fMRI. *Neuroimage*, 20(2), 1384-1392.
- Lemieux, L., Salek-Haddadi, A., Josephs, O., Allen, P., Toms, N., Scott, C., et al. (2001). Event-related fMRI with simultaneous and continuous EEG: description of the method and initial case report. *Neuroimage*, 14(3), 780-787.
- Li, C. S., Yan, P., Sinha, R., & Lee, T. W. (2008). Subcortical processes of motor response inhibition during a stop signal task. *Neuroimage*, 41(4), 1352-1363.
- Li, S. C. (2005). Neurocomputational Perspectives Linking Neuromodulation, Processing Noise, Representational Distinctiveness, and Cognitive Aging. In R. Cabeza, L. Nyberg & D. Park (Eds.), *Cognitive Neuroscience of Aging: Linking Cognitive and Cerebral Aging*. New York: Oxford University Press.

- Liotti, M., Woldorff, M. G., Perez, R., & Mayberg, H. S. (2000). An ERP study of the temporal course of the Stroop color-word interference effect. *Neuropsychologia*, 38(5), 701-711.
- Logan, J. M., Sanders, A. L., Snyder, A. Z., Morris, J. C., & Buckner, R. L. (2002). Under-recruitment and nonselective recruitment: dissociable neural mechanisms associated with aging. *Neuron*, 33(5), 827-840.
- Logie, R. H. (1995). *Visuo-spatial working memory*. UK: Erbaum.
- Lupyan, G., Thompson-Schill, S. L., & Swingle, D. (2010). Conceptual penetration of visual processing. *Psychological Science*, 21(5), 682-691.
- Lustig, C., May, C. P., & Hasher, L. (2001). Working memory span and the role of proactive interference. *Journal of Experimental Psychology*, 130(2), 199-207.
- MacDonald, A. W., Cohen, J., Stenger, V. A., & Carter, C. S. (2000). Dissociating the Role of the Dorsolateral Prefrontal and Anterior Cingulate Cortex in Cognitive Control. *Science*, 288, 1835-1838.
- Madden, D. J., Turkington, T. G., Provenzale, J. M., Hawk, T. C., Hoffman, J. M., & Coleman, R. E. (1997). Selective and divided visual attention: age-related changes in regional cerebral blood flow measured by H2(15)O PET. *Human Brain Mapping*, 5(6), 389-409.
- Makeig, S., Bell, A. J., Jung, T. P., & Sejnowski, T. J. (1996). Independent component analysis of electroencephalographic data. In D. Touretzky, M. Mozer & N. Hasselmo (Eds.), *Advances in neuron information processing systems* (pp. 145-151).
- Makeig, S., Debener, S., Onton, J., & Delorme, A. (2004). Mining event-related brain dynamics. *Trends in Cognitive Science*, 8(5), 204-210.
- Makeig, S., Westerfield, M., Jung, T. P., Covington, J., Townsend, J., Sejnowski, T. J., et al. (1999). Functionally independent components of the late positive event-related potential during visual spatial attention. *Journal of Neuroscience*, 19(7), 2665-2680.
- Mansouri, F. A., Tanaka, K., & Buckley, M. J. (2009). Conflict-induced behavioural adjustment: a clue to the executive functions of the prefrontal cortex. *Nature Reviews Neuroscience*, 10(2), 141-152.

- Markela-Lerenc, J., Ille, N., Kaiser, S., Fiedler, P., Mundt, C., & Weisbrod, M. (2004). Prefrontal-cingulate activation during executive control: which comes first? *Brain Research*, 18(3), 278-287.
- Markela-Lerenc, J., Ille, N., Kaiser, S., Fiedler, P., Mundt, C., & Weisbrod, M. (2004). Prefrontal-cingulate activation during executive control: which comes first? *Brain Res Cognitive Brain Research*, 18(3), 278-287.
- McDowd, J. M. (1997). Inhibition in attention and aging. *Journal of Gerontology*, 52(6), P265-273.
- Mecklinger, A., Weber, K., Gunter, T. C., & Engle, R. W. (2003). Dissociable brain mechanisms for inhibitory control: effects of interference content and working memory capacity. *Cognitive Brain Research*, 18(1), 26-38.
- Milham, M. P., Banich, M. T., & Barad, V. (2003). Competition for priority in processing increass prefrontal cortex's involvement in top-down control: an event-related fMRI study of the Stroop task. *Cognitive Brain Research*, 17, 212-222.
- Milham, M. P., Banich, M. T., Webb, A., Barad, V., Cohen, N. J., Wszalek, T., et al. (2001). The Relative Involment of Anterior Cingulate and Prefrontal Cortex in Attentional Control Depends on Nature of Conflict. *Cognitive Brain Research*, 12, 467-473.
- Milham, M. P., Erickson, K. I., Banich, M. T., Kramer, A. F., Webb, A., Wszalek, T., et al. (2001). Attentional control in the aging brain: Insights from an fMRI study of the stroop task. *Brain and Cognition*, 49, 277-296.
- Miller, B. T., & D'Esposito, M. (2005). Searching for "the top" in top-down control. *Neuron*, 48(4), 535-538.
- Miller, E. K. (2000). The prefrontal cortex and cognitive control. *Nature Reviews Neuroscience*, 1(1), 59-65.
- Miller, G. A., Galanter, E. & Pigram, K. H. (1960). *Plans and the structure of behaviour*. New York: Henry Holt and Company.
- Milner, B., Petrides, M. & Smith, M. L. (1985). Frontal lobes and the temporal organization of memory. *Human Neurobiology*, 4, 137-142.

- Miyake, A., Friedman, N. P., Rettinger, D. A., Shah, P., & Hegarty, M. (2001). How are visuospatial working memory, executive functioning, and spatial abilities related? A latent-variable analysis. *Journal of Experimental Psychology*, 130(4), 621-640.
- Monsell, S. (1978). Recency, immediate recognition, and reaction time. *Cognitive Psychology*, 10, 465-501.
- Morcom, A. M., & Fletcher, P. C. (2007). Does the brain have a baseline? Why we should be resisting a rest. *Neuroimage*, 37, 1073-1082.
- Morris, R. G., Gick, M. L., & Craik, F. I. (1988). Processing resources and age differences in working memory. *Memory and Cognition*, 16(4), 362-366.
- Müller, N. G., & Knight, R. T. (2006). The functional neuroanatomy of working memory: Contributions of human brain lesion studies. *Neuroscience*, 139, 51-58.
- Narayanan, N. S., Prabhakaran, v., Bunge, S. A, Christoff, K, Fine, M. & Gabrieli, D. E. (2005). The Role of the Prefrontal Cortex in the Maintenance of Verbal Working Memory: An Event-Related tMRI Analysis. *Neuropsychology*, 19, 223-232.
- Nee, D. E., Jonides, J., & Berman, M. G. (2007). Neural mechanisms of proactive interference-resolution. *Neuroimage*, 38(4), 740-751.
- Nelson, J. K., Reuter-Lorenz, P. A., Persson, J., Sylvester, C. Y., & Jonides, J. (2009). Mapping interference resolution across task domains: a shared control process in left inferior frontal gyrus. *Brain Research*, 1256, 92-100.
- Nelson, K., Reuter-Lorenz, P. A., Sylvester, C. Y. C., Jonides, J., & Smith, E. (2003). Dissociable neural mechanisms underlying response-based and familiarity-based conflict in working memory. *PNAS*, 100, 11171-11175.
- Newman, S. D., Twieg, D. B., & Carpenter, P. A. (2001). Baseline conditions and subtractive logic in neuroimaging. *Human Brain Mapping*, 14, 228-235.
- Nielson, K. A., Langenecker, S. A., & Garavan, H. (2002). Differences in the functional neuroanatomy of inhibitory control across the adult life span. *Psychology of Aging*, 17(1), 56-71.
- Nieuwenhuis, S., Aston-Jones, G., & Cohen, J. D. (2005). Decision making, the P3, and the locus coeruleus-norepinephrine system. *Psychological Bulletin*, 131(4), 510-532.

- Nieuwenhuis, S., Yeung, N., van den Wildenberg, W., & Ridderinkhof, K. R. (2003). Electrophysiological correlates of anterior cingulate function in a go/no-go task: effects of response conflict and trial type frequency. *Cognitive, Affect, and Behavioral Neuroscience*, 3(1), 17-26.
- Norman, D. A., & Shallice, T. (1986). Attention to action: willed and automatic control of behaviour. In G. E. Schwartz & D. Shapiro (Eds.), *Consciousness and self-regulation* (Vol. 4). New York: Plenum Press.
- Nyberg, L., Backman, L., Erngrund, K., Olofsson, U., & Nilsson, L. G. (1996). Age differences in episodic memory, semantic memory, and priming: relationships to demographic, intellectual, and biological factors. *Journal of Gerontology*, 51(4), P234-240.
- Park, D. C. (2000). The basic mechanisms accounting for age-related decline in cognitive function. In D. Park & N. Schwarz (Eds.), *Cognitive Aging: A Primer* (pp. 1-22). Philadelphia: Psychology Press.
- Park, D. C., Polk, T. A., Park, R., Minear, M., Savage, A., & Smith, M. R. (2004). Aging reduces neural specialization in ventral visual cortex. *PNAS*, 101(35), 13091-13095.
- Park, D. C., Welsh, R. C., Marshuetz, C., Gutchess, A. H., Mikels, J., Polk, T. A., et al. (2003). Working memory for complex scenes: age differences in frontal and hippocampal activations. *Journal of Cognitive Neuroscience*, 15(8), 1122-1134.
- Pascual-Marqui, R. D., Esslen, M., Kochi, K., & Lehmann, D. (2002). Functional imaging with low-resolution brain electromagnetic tomography (LORETA): a review. *Experimental Clinical Pharmacology*, 24 Suppl C, 91-95.
- Peiffer, A. M., Hugenschmidt, C. E., Maldjian, J. A., Casanova, R., Srikanth, R., Hayasaka, S., et al. (2009). Aging and the interaction of sensory cortical function and structure. *Human Brain Mapping*, 30(1), 228-240.
- Perret, E. (1974). The left frontal lobe of man and the suppression of habitual responses in verbal categorical behaviour. *Neuropsychology*, 12, 323-330.
- Polich, J. (2007). Updating P300: an integrative theory of P3a and P3b. *Clinical Neurophysiology*, 118(10), 2128-2148.

- Polich, J., & Criado, J. R. (2006). Neuropsychology and neuropharmacology of P3a and P3b. *International Journal of Psychophysiology*, 60(2), 172-185.
- Postle, B. R., Brush, L. N., & Nick, A. M. (2004). Prefrontal cortex and the mediation of proactive interference in working memory. *Cognitive and Affective Neuroscience*, 4, 600-608.
- Quintana, J. & Fuster, J. M. (1999). From Perception to Action: Temporal Integrative Functions of Prefrontal and Parietal Neurons. *Cerebral Cortex*, 9, 213-221.
- Raichle, M. E., MacLeod, A. M., Snyder, A. Z., Powers, W. J., Gusnard, D. A., & Shulman, G. L. (2001). A default mode of brain function. *PNAS*, 98, 676-682.
- Rapp, P. R., & Amaral, D. G. (1992). Individual differences in the cognitive and neurobiological consequences of normal aging. *Trends Neuroscience*, 15(9), 340-345.
- Raz, N. (1999). Aging of the brain and its impact on cognitive performance: Integration of structural and functional findings. In F. I. M. Craik & T. A. Salthouse (Eds.), *Handbook of Aging and Cognition*. Mahwah, NJ: Erlbaum.
- Raz, N., Ghisletta, P., Rodrigue, K. M., Kennedy, K. M., & Lindenberger, U. (2010). Trajectories of brain aging in middle-aged and older adults: regional and individual differences. *Neuroimage*, 51(2), 501-511.
- Raz, N., Rodrigue, K. M., Kennedy, K. M., & Acker, J. D. (2007). Vascular health and longitudinal changes in brain and cognition in middle-aged and older adults. *Neuropsychology*, 21(2), 149-157.
- Rebai, M., Bernard, C., & Lannou, J. (1997). The Stroop's test evokes a negative brain potential, the N400. *International Journal of Neuroscience*, 91(1-2), 85-94.
- Repovš, G., & Baddeley, A. D. (2006). The multi-component model of working memory: explorations in experimental cognitive psychology. *Neuroscience*, 139, 5-21.
- Reuter-Lorenz, P. (2002). New visions of the aging mind and brain. *Trends Cogn Sci*, 6(9), 394.
- Reuter-Lorenz, P. A., Jonides, J., Smith, E. E., Hartley, A., Miller, A., Marshuetz, C., et al. (2000). Age differences in the frontal lateralization of verbal and spatial

- working memory revealed by PET. *Journal of Cognitive Neuroscience*, 12(1), 174-187.
- Reuter-Lorenz, P. A., & Lustig, C. (2005). Brain aging: reorganizing discoveries about the aging mind. *Current Opinion in Neurobiology*, 15(2), 245-251.
- Ridderinkhof, K. R., Nieuwenhuis, S., & Braver, T. S. (2007). Medial frontal cortex function: an introduction and overview. *Cognitive, Affective, and Behavioral Neuroscience*, 7(4), 261-265.
- Ridderinkhof, K. R., Ullsperger, M., Crone, E. A., & Nieuwenhuis, S. (2004). The role of the medial frontal cortex in cognitive control. *Science*, 306(5695), 443-447.
- Ridderinkhof, K. R., van den Wildenberg, W. P., Segalowitz, S. J., & Carter, C. S. (2004). Neurocognitive mechanisms of cognitive control: the role of prefrontal cortex in action selection, response inhibition, performance monitoring, and reward-based learning. *Brain and Cognition*, 56(2), 129-140.
- Rosen, A. C., Prull, M. W., O'Hara, R., Race, E. A., Desmond, J. E., Glover, G. H., et al. (2002). Variable effects of aging on frontal lobe contributions to memory. *Neuroreport*, 13(18), 2425-2428.
- Rushworth, M. F. S., Walton, M. E., Kennerley, S. W., & Bannerman, D. M. (2004). Action sets and decisions in the medial frontal cortex. *Trends in Cognitive Neurosciences*, 8, 410-417.
- Rutman, A. M., Clapp, W. C., Chadick, J. Z., & Gazzaley, A. (2010). Early top-down control of visual processing predicts working memory performance. *Journal of Cognitive Neuroscience*, 22(6), 1224-1234.
- Rypma, B., & D'Esposito, M. (2000). Isolating the neural mechanisms of age-related changes in human working memory. *Nature Neuroscience*, 3(5), 509-515.
- Salat, D. H., Buckner, R. L., Snyder, A. Z., Greve, D. N., Desikan, R. S., Busa, E., et al. (2004). Thinning of the cerebral cortex in aging. *Cerebral Cortex*, 14(7), 721-730.
- Salat, D. H., Tuch, D. S., Hevelone, N. D., Fischl, B., Corkin, S., Rosas, H. D., et al. (2005). Age-related changes in prefrontal white matter measured by diffusion tensor imaging. *Annals of the New York Academy of Science*, 1064, 37-49.
- Salthouse, T. A. (1988). The role of processing resources in cognitive aging. In M.L. Howe & C.J. Brainard (Eds.), *Cognitive development in adulthood* (185-239).

New York: Springer-Verlag.

- Salthouse, T. A. & Meinz, E. (1995). Aging, Inhibition, Working Memory, and Speed. *Journal of Gerontology*, 50, 297-305.
- Salthouse, T. A. (1996). The processing-speed theory of adult age differences in cognition. *Psychological Review*, 103(3), 403-428.
- Salthouse, T. A. (2000). Aging and measures of processing speed. *Biological Psychology*, 54(1-3), 35-54.
- Salthouse, T. A. (2009). When does age-related cognitive decline begin? *Neurobiology of Aging*, 30(4), 507-514.
- Salthouse, T. A., Atkinson, T. M., & Berish, D. E. (2003). Executive functioning as a potential mediator of age-related cognitive decline in normal adults. *Journal of Experimental Psychology*, 132(4), 566-594.
- Sambataro, F., Murty, V. P., Callicott, J. H., Tan, H. Y., Das, S., Weinberger, D. R., et al. (2010). Age-related alterations in default mode network: impact on working memory performance. *Neurobiology of Aging*, 31(5), 839-852.
- Schneider-Garces, N. J., Gordon, B. A., Brumback-Peltz, C. R., Shin, E., Lee, Y., Sutton, B. P., et al. (2010). Span, CRUNCH, and beyond: working memory capacity and the aging brain. *Journal of Cognitive Neuroscience*, 22(4), 655-669.
- Segalowitz, S. J., & Davies, P. L. (2004). Charting the maturation of the frontal lobe: an electrophysiological strategy. *Brain and Cognition*, 55(1), 116-133.
- Segalowitz, S. J., Van Roon, P., & Dywan, J. (1997). The ERP late positivity: a graduated response to stimulus repetition. *Neuroreport*, 8(3), 757-760.
- Shallice, T., & Burgess, P. (1996). The domain of supervisory processes and temporal organization of behaviour. *Philosophical Transactions of the Royal Society*, 351(1346), 1405-1411; discussion 1411-1402.
- Shilling, V. M., Chetwynd, A., & Rabbitt, P. M. (2002). Individual inconsistency across measures of inhibition: an investigation of the construct validity of inhibition in older adults. *Neuropsychologia*, 40(6), 605-619.
- Silton, R. L., Heller, W., Towers, D. N., Engels, A. S., Spielberg, J. M., Edgar, J. C., et al. (2010). The time course of activity in dorsolateral prefrontal cortex and anterior

- cingulate cortex during top-down attentional control. *Neuroimage*, 50(3), 1292-1302.
- Solbakk, A. K., Fuhrmann Alpert, G., Furst, A. J., Hale, L. A., Oga, T., Chetty, S., et al. (2008). Altered prefrontal function with aging: insights into age-associated performance decline. *Brain Research*, 1232, 30-47.
- Stemmer, B., Segalowitz, S. J., Witzke, W., & Schönle, P. W. (2004). Error detection in patients with lesions to the medial prefrontal cortex: an ERP study. *Neuropsychologia*, 42(1), 118-130.
- Sternberg, S. (1966). High-speed scanning in human memory. *Science*, 153, 652-654.
- Sternberg, S. (1969). The discovery of processing stages: Extensions of Donders' Method. *Acta Psychologica*, 30, 276-315.
- Sullivan, E. V., & Pfefferbaum, A. (2006). Diffusion tensor imaging and aging. *Neuroscience and Biobehavioral Reviews*, 30(6), 749-761.
- Swick, D., & Turken, A. U. (2002). Dissociation between conflict detection and error monitoring in the human anterior cingulate cortex. *PNAS*, 99, 16354-16359.
- Tays, W. J., Dywan, J., Mathewson, K. J., & Segalowitz, S. J. (2008). Age differences in target detection and interference resolution in working memory: An event-related potential study. *Journal of Cognitive Neuroscience*, 20, 2250-2262.
- Tays, W. J., Dywan, J., & Segalowitz, S. J. (2009). General proactive interference and the N450 response. *Neuroscience Letters*, 462(3), 239-243.
- Thompson-Schill, S.L., D'Esposito, M., Aguirre, G.K. & Farah, G.K. (1997). Role of the left inferior prefrontal cortex in retrieval of semantic knowledge: a reevaluation. *Proc Nat Acad Sci USA*, 94, 14792-14797.
- Thompson-Schill, S. L., Jonides, J., Marshuetz, C., Smith, E. E., D'Esposito, M., Kan, I. P., et al. (2002). Effects of frontal lobe damage on interference effects in working memory. *Cognitive, Affective, and Behavioral Neuroscience*, 2(2), 109-120.
- Underwood, B. J. (1957). Interference and forgetting. *Psychological Review*, 64, 49-60.
- Van Boxtel, G. J. M. (2004). The use of the subtraction technique in the psychophysiology of response inhibition and conflict. In M. Ullsperger & M. Falkenstein (Eds.), *Errors, Conflict, and the Brain. Current Opinions on*

- Performance Monitoring* (pp. 219-225). Leipzig: Max Planck Institute for Human Cognitive and Brain Sciences.
- van Gaal, S., Lamme, V. A., Fahrenfort, J. J., & Ridderinkhof, K. R. (2010). Dissociable Brain Mechanisms Underlying the Conscious and Unconscious Control of Behavior. *Journal of Cognitive Neuroscience*, 23, 91-105.
- van Gaal, S., Ridderinkhof, K. R., Scholte, H. S., & Lamme, V. A. (2010). Unconscious activation of the prefrontal no-go network. *Journal of Neuroscience*, 30(11), 4143-4150.
- van Veen, V., & Carter, C. S. (2002). The anterior cingulate as a conflict monitor: fMRI and ERP studies. *Physiology and Behavior*, 77(4-5), 477-482.
- Velanova, K., Lustig, C., Jacoby, L. L., & Buckner, R. L. (2007). Evidence for frontally mediated controlled processing differences in older adults. *Cerebral Cortex*, 17(5), 1033-1046.
- Verhaeghen, P., & Cerella, J. (2002). Aging, executive control, and attention: a review of meta-analyses. *Neuroscience and Biobehavioral Reviews*, 26(7), 849-857.
- Volkow, N. D., Logan, J., Fowler, J. S., Wang, G. J., Gur, R. C., Wong, C., et al. (2000). Association between age-related decline in brain dopamine activity and impairment in frontal and cingulate metabolism. *American Journal of Psychiatry*, 157(1), 75-80.
- Wager, T. D., Sylvester, C. Y., Lacey, S. C., Nee, D. E., Franklin, M., & Jonides, J. (2005). Common and unique components of response inhibition revealed by fMRI. *Neuroimage*, 27(2), 323-340.
- Walhovd, K. B., Fjell, A. M., Reinvang, I., Lundervold, A., Fischl, B., Quinn, B. T., et al. (2006). The functional and structural significance of the frontal shift in the old/new ERP effect. *Brain Research*, 1081(1), 156-170.
- Walton, M. E., Croxson, P. L., Behrens, T. E. J., Kennerley, S. W., & Rushworth, M. F. S. (2007). Adaptive decision making and value in the anterior cingulate cortex. *Neuroimage*, 36, 142-154.
- Weissman, D. H., Gopalakrishnan, A., Hazlett, C. J., & Woldorf, W. G. (2005). Dorsal anterior cingulate cortex resolves conflict from distracting stimuli by boosting attention toward relevant events. *Cerebral Cortex*, 15, 229-237.

- West, R. (1996). An application of prefrontal cortex function theory to cognitive aging. *Psychological Bulletin*, 120(2), 272-292.
- West, R. (2003). Neural correlates of cognitive control and conflict detection in the Stroop and digit-location tasks. *Neuropsychologia*, 41(8), 1122-1135.
- West, R. (2004). The effects of aging on controlled attention and conflict processing in the Stroop task. *Journal of Cognitive Neuroscience*, 16, 103-113.
- West, R., & Alain, C. (1999). Event-related neural activity associated with the Stroop task. *Cognitive Brain Research*, 8(2), 157-164.
- West, R., & Alain, C. (2000). Effects of task context and fluctuations of attention on neural activity supporting performance of the Stroop task. *Brain Research*, 873, 102-111.
- West, R., Bowry, R., & McConville, C. (2004). Sensitivity of medial frontal cortex to response and nonresponse conflict. *Psychophysiology*, 41(5), 739-748.
- West, R., Jakubek, K., Wymbs, N., Perry, M., & Moore, K. (2005). Neural correlates of conflict processing. *Experimental Brain Research*, 167, 38-48.
- West, R., & Schwarb, H. (2006). The influence of aging and frontal function on the neural correlates of regulative and evaluative control. *Neuropsychology*, 20, 468-481.
- West, R. L. (1996). An application of prefrontal cortex function theory to cognitive aging. *Psychological Bulletin*, 120(2), 272-292.
- Wickens, D. D., Born, D. G., & Allen, C. K. (1963). Proactive inhibition and item similarity in short-term memory. *Journal of Verbal Learning & Verbal Behavior*, 2, 440-445.
- Wilding, E. L. (2000). In what way does the parietal ERP old/new effect index recollection? *International Journal of Psychophysiology*, 35(1), 81-87.
- Witney, P., Arnett, P. A., Driver, A., & Budd, D. (2001). Measuring central executive functioning: what's in a reading span? *Brain and Cognition*, 45, 1-14.
- Wolk, D. A., Sen, N. M., Chong, H., Riis, J. L., McGinnis, S. M., Holcomb, P. J., et al. (2009). ERP correlates of item recognition memory: effects of age and performance. *Brain Research*, 1250, 218-231.

Yeung, N., & Nieuwenhuis, S. (2009). Dissociating response conflict and error likelihood in anterior cingulate cortex. *Journal Neuroscience*, 29(46), 14506-14510.

Tables

Table 2.1. Examples of condition manipulations. Boldface highlights PI manipulations. Underlining highlights an example of general stimulus repetition and can only occur in small stimulus set trials.

Trial	Memory Set		Probe	Condition Type
n-3	<u>edge</u> ride trap link			
n-2	tune link dash ace			
n-1	dash hill kid vote		VOTE	
n	day rain film kid	if	FILM	Positive
		if	<u>EDGE</u>	Negative
		if	HILL	Negative/Familiar
		if	DASH	Negative/High Familiar
		if	VOTE	Negative/Response Conflict

Table 2.2. Mean N450 amplitudes (*Amp*) for each condition of the large and small set size tasks. Contrasts between the negative condition and each PI condition are given with associated standard errors (*SE*).

Condition	Large Set Size			Small Set Size		
	Amp	(SE)	Contrast	Amp	(SE)	Contrast
Negative	0.52	(.48)		-1.48	(.51)	
Familiar	-0.73	(.60)	-1.25*	-1.84	(.48)	-0.36
High-Fam.	-0.80	(.56)	-1.32*	-1.92	(.44)	-0.44
Resp. Con.	-0.86	(.54)	-1.38*	-2.49	(.58)	-1.01*

*p<.01

Table 3.1 – Mean percent accuracy and response times (ms) associated with old and new probes in the simple Sternberg task and percent accuracy associated with the incidental memory task. Standard error values are presented in brackets.

Group	Simple Sternberg Task				Incidental Memory
	Old Probe		New Probe		% Accuracy
	% Accuracy	RT	% Accuracy	RT	
Younger	94.9 (1.2)	675 (28)	96.6 (0.6)	680 (23)	71.2 (1.9)
Older	94.4 (1.1)	845 (33)	96.3 (0.9)	838 (27)	63.8 (1.6)

Table 3.2 Mean amplitudes (μV) and standard error of the difference scores for key statistical analyses relating to the present hypotheses. (EPN = early posterior negativity and FP = frontal positivity)

Task		Younger Adults			Older Adults		
		Old	New	SE _D	Old	New	SE _D
Stemberg	EPN	-2.07	-0.77	0.52	0.35	0.82	0.63
	FP	-2.03	-0.81	0.68	1.96	2.10	0.61
	P3b	4.76	2.96	0.34	1.96	0.64	0.44
Incidental Memory	FP	-0.56	-0.29	0.42	1.23	0.75	0.30
	P3b	3.26	2.18	0.30	0.86	0.81	0.55

Table 4.1 Mean percentage error rates with standard error values (SE) for each condition at each level of working memory load

	Condition							
	Positive		Negative		Familiar		Resp. Conflict	
Load	<i>M</i>	<i>SE</i>	<i>M</i>	<i>SE</i>	<i>M</i>	<i>SE</i>	<i>M</i>	<i>SE</i>
Low	4.8	.56	1.5	.48	2.1	.60	5.7	1.49
Medium	8.9	1.84	2.8	.68	9.2	1.62	8.0	1.74
High	12.8	1.85	3.2	1.11	15.9	1.87	18.2	2.73

Table 4.2 Mean response times (milliseconds) with standard error values (SE) for each condition at each level of working memory load

Load	Condition							
	Positive		Negative		Familiar		Resp. Conflict	
	<i>M</i>	<i>SE</i>	<i>M</i>	<i>SE</i>	<i>M</i>	<i>SE</i>	<i>M</i>	<i>SE</i>
Low	532	20	540	21	589	34	598	27
Medium	613	32	597	34	684	44	686	38
High	659	34	627	29	689	37	721	36

Table 4.3. Mean N450 amplitudes from select frontal sites for each the neutral and combined PI conditions at each working memory load. Mean differences (and standard errors of the difference) are shown beneath each contrast.

Load	Sensor Site					
	F5 (Left)		Fz (Central)		F6 (Right)	
	Neutral	PI	Neutral	PI	Neutral	PI
Low	0.89	-1.36	-.11	-1.94	-1.33	-1.16
	Diff= -2.25* (.71)		Diff= -1.83 (.87)		Diff= -.17 (.46)	
Medium	-0.58	-1.08	-1.16	-0.90	-1.45	-1.92
	Diff= -.50 (.72)		Diff= .26 (.71)		Diff= .47 (.41)	
High	0.12	0.07	1.81	-0.09	1.30	-0.82
	Diff= -.19 (.73)		Diff= -1.90* (.63)		Diff= -2.12 (.56)*	

* $p < .05$

Table 4.4. Mean N450_{ICA} amplitudes from select frontal sites for each the neutral and combined PI conditions and each working memory load. Mean differences (and standard errors of the difference) are shown beneath each contrast.

Load	Sensor Site					
	F5 (Left)		Fz (Central)		F6 (Right)	
	Neutral	PI	Neutral	PI	Neutral	PI
Low	.64	-.44	.43	-.53	.04	-.29
	Diff = -1.08 (.34)*		Diff = -.96 (.38)		Diff = -.33 (.39)	
Medium	.44	-.29	.68	-.41	.45	-.31
	Diff = -.73 (.46)		Diff = -1.09 (.33)*		Diff = -.76 (.41)	
High	.39	-.18	.81	-.44	.38	-.71
	Diff = -.57 (.42)		Diff = -1.25 (.39)*		Diff = -1.09 (.31)*	

Note: * $p < .01$

Figures

Figure 2.1

A schematic diagram of the procedure

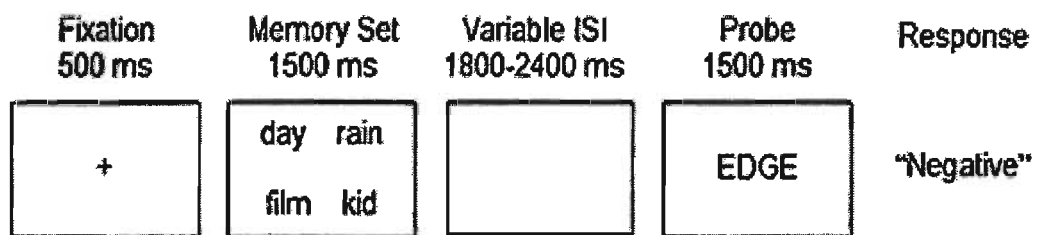


Figure 2.2

Behavioral data for small and large set size tasks.

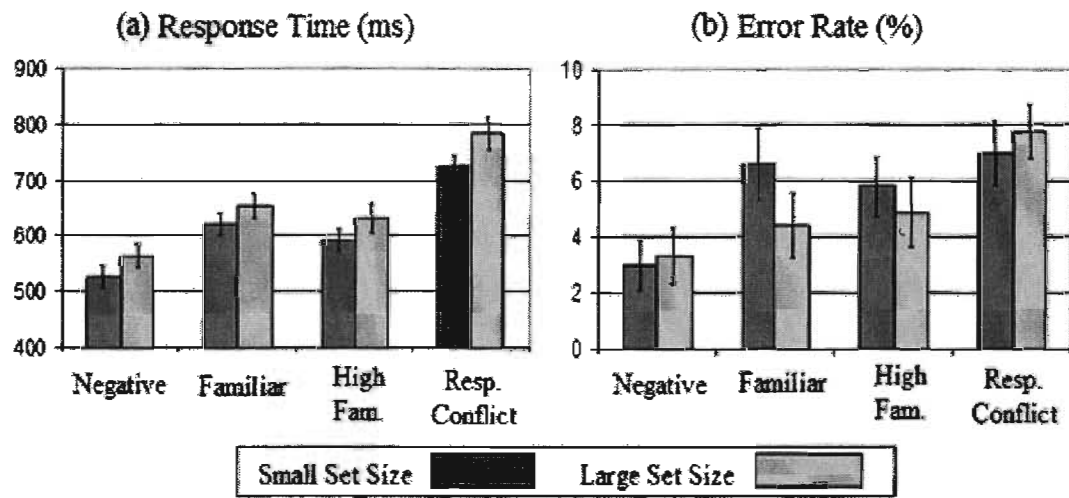
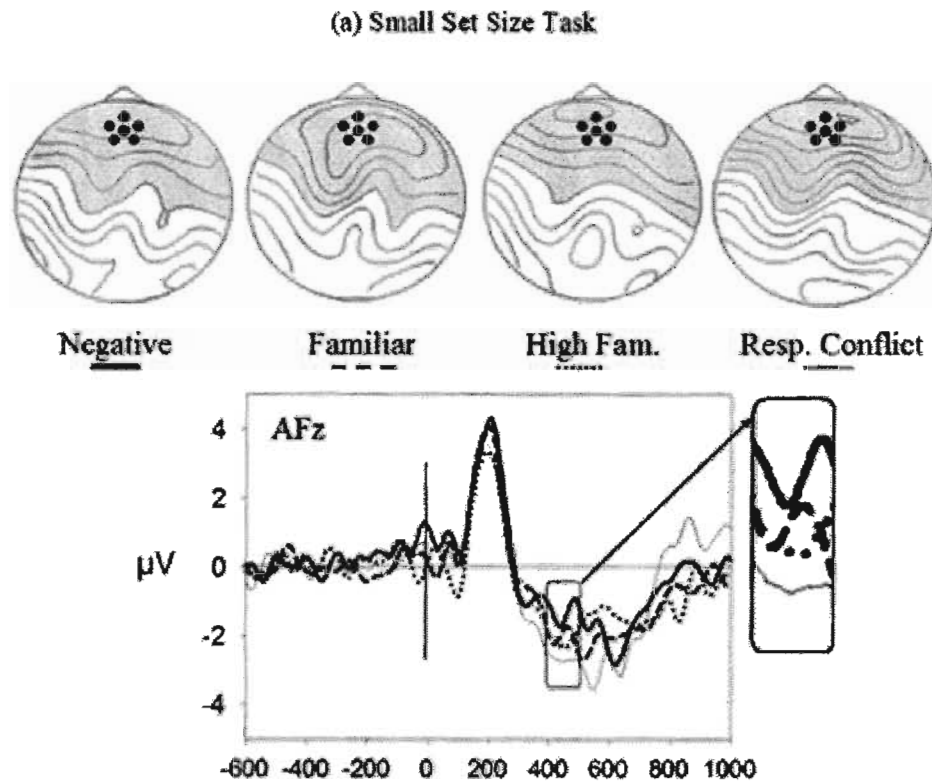


Figure 2.3

Scalp potentials at approximately 450 ms following the probe for the small set size (3a) and for the large set size (3b). The analyzed cluster of sensors are highlighted in black centered around AFz. Negativities appear in grey (.25 μV per step).



(b) Large Set Size Task

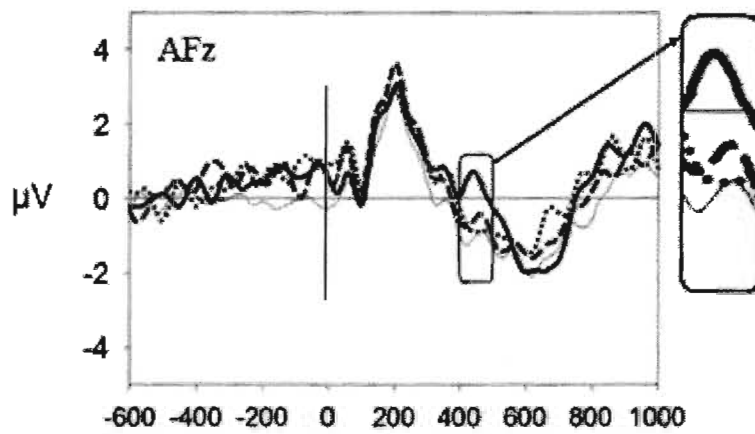
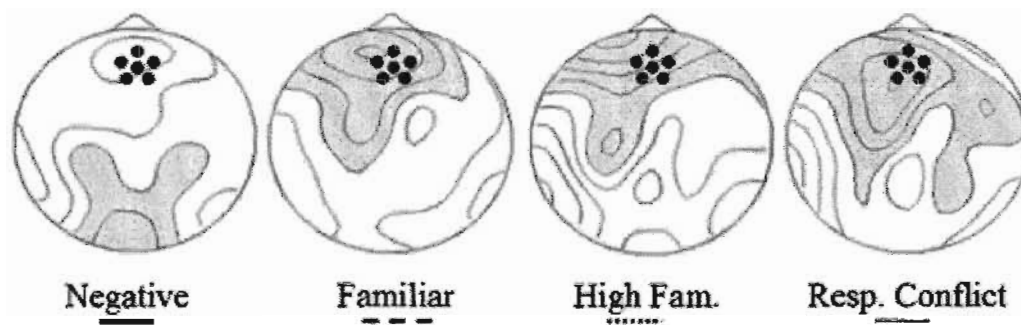


Figure 3.1
Experimental procedure for the Sternberg task and incidental memory task.

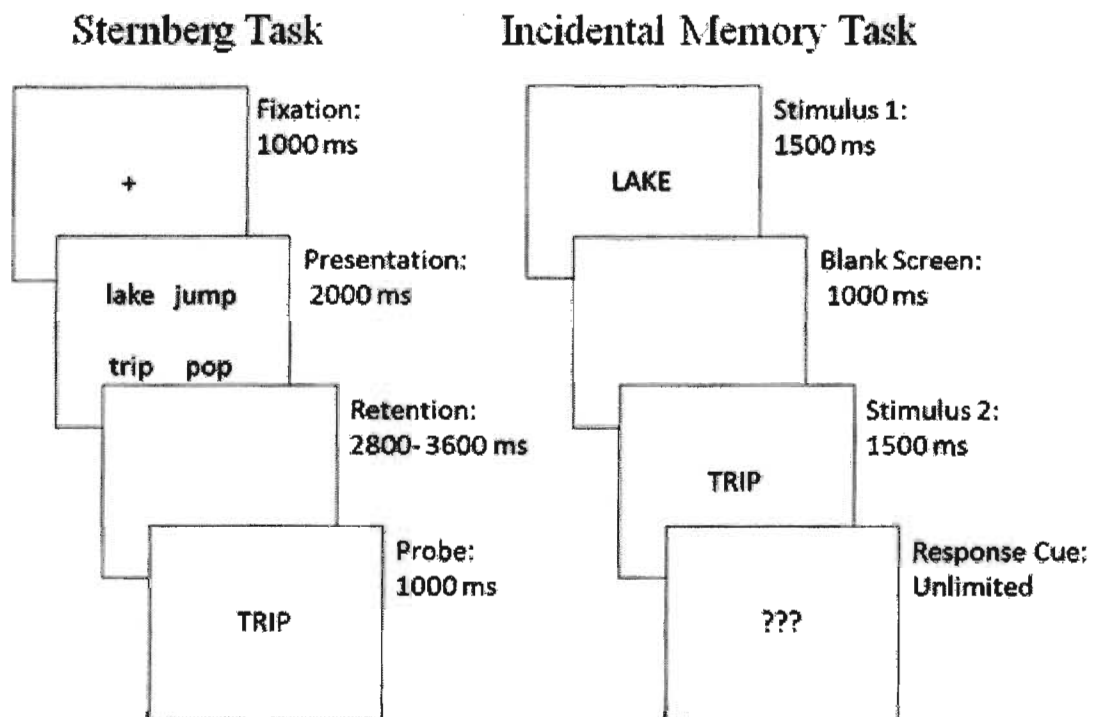


Figure 3.2a

Selected stimulus-locked, grand-averaged waveforms for correctly identified old and new probes in the Sternberg task. (EPN = Early Posterior Negativity & FP = frontal positivity)

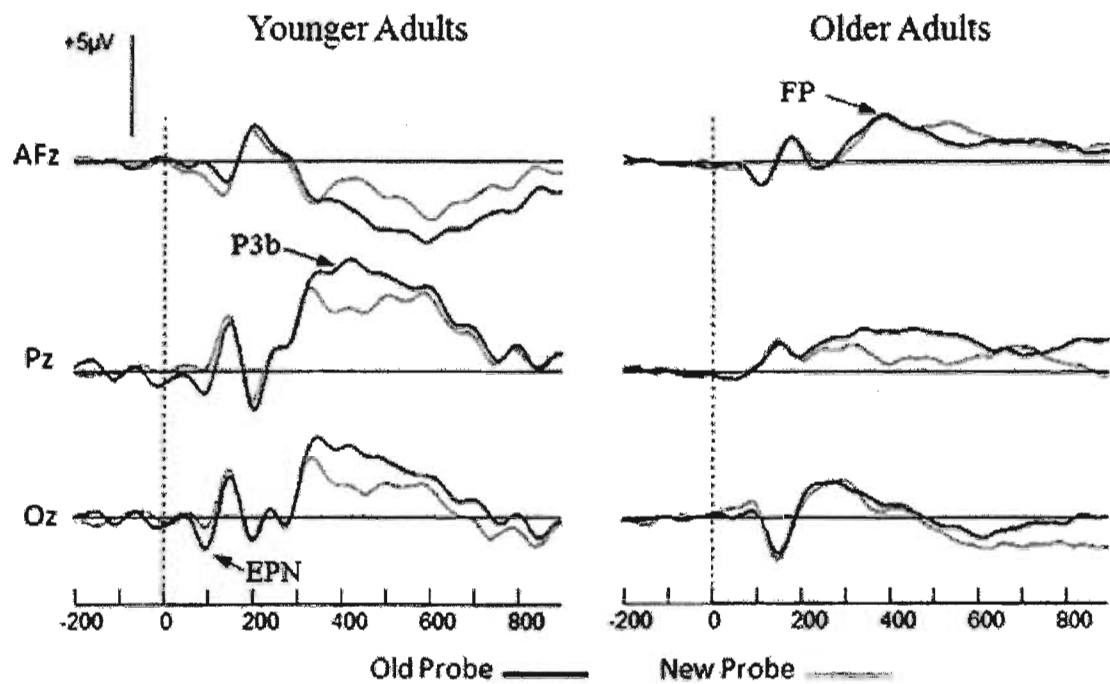


Figure 3.2b

Selected stimulus-locked, grand-averaged waveforms for correctly identified old and new stimuli in incidental memory task. (FP = frontal positivity)

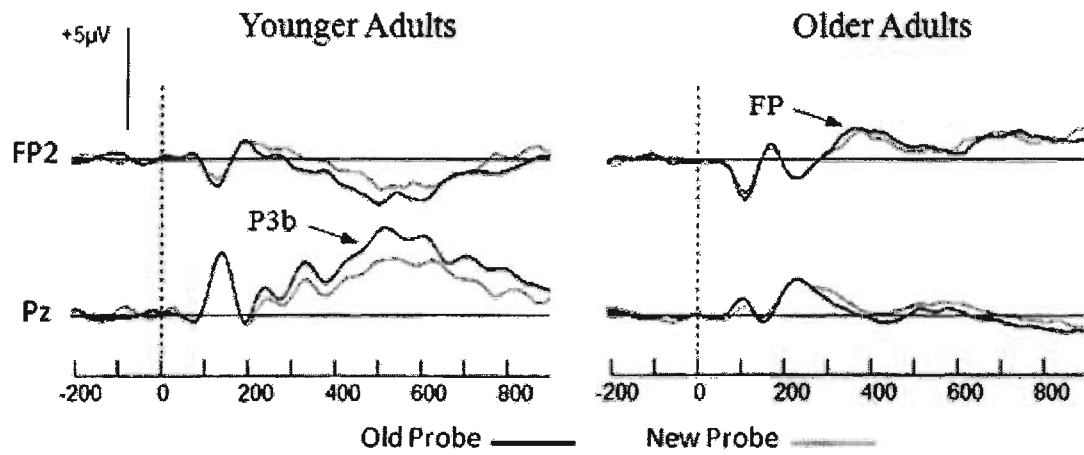


Figure 3.3

A top-down view of ERP topographies for the early posterior negativity and frontal positivity in younger and older adults during the Sternberg task. The top of each map corresponds to the front of the electrode net. Positivities are in white and negativities appear as dark gray with topographic lines representing successive increases in amplitude of $\pm 0.5 \mu V$.

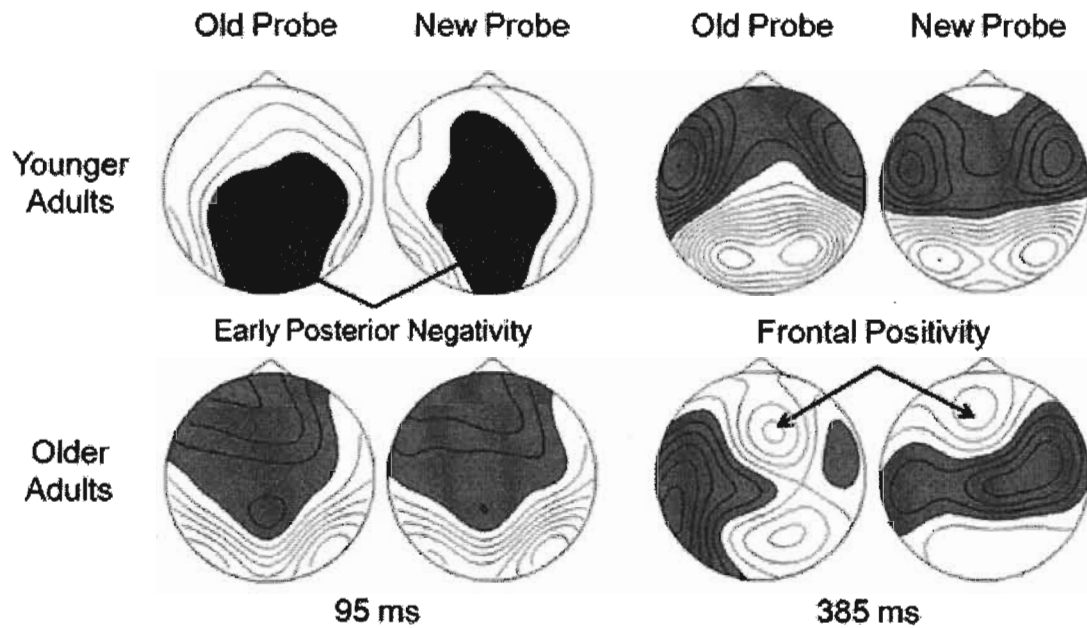


Figure 3.4

The scatterplot of the linear relationship between mean Sternberg accuracy and mean frontal positivity values in older adults.

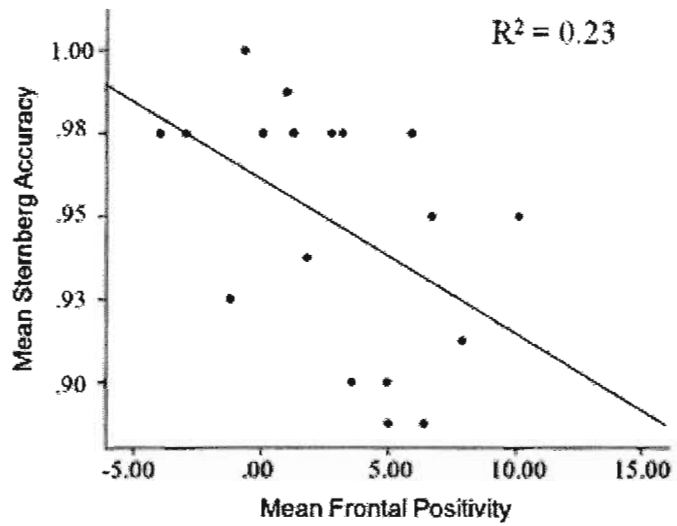


Figure 3.5

The scatterplot of the linear relationship of mean standardized residualised early posterior negativity (old probe with new probe partialled out) with a) mean Sternberg accuracy, and b) mean Sternberg RT.

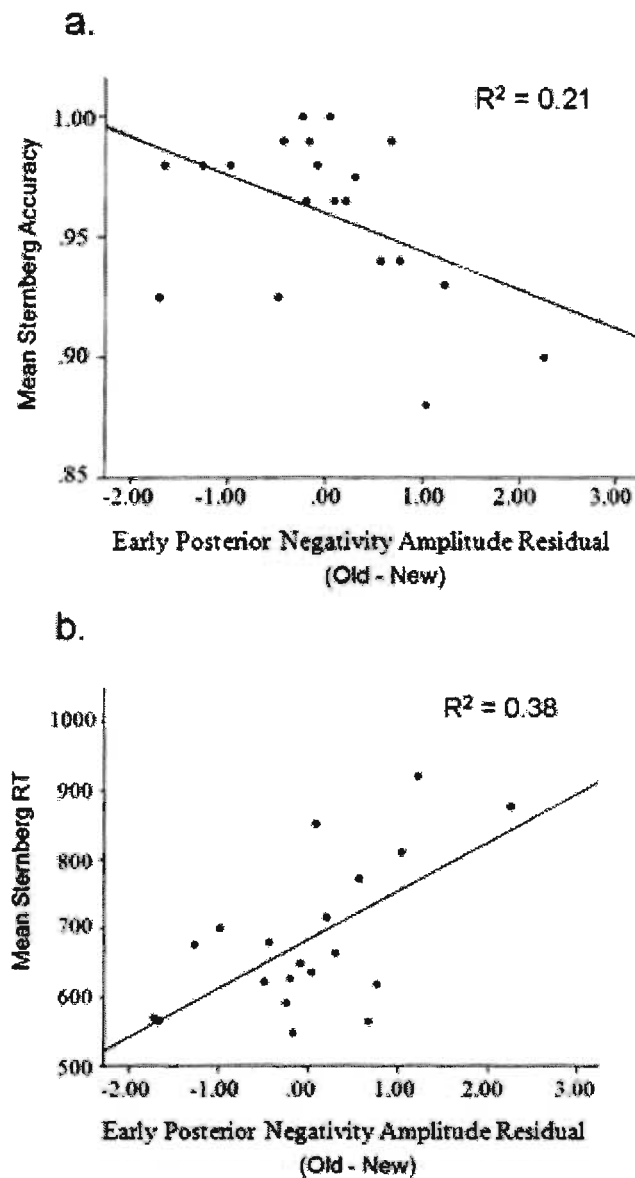
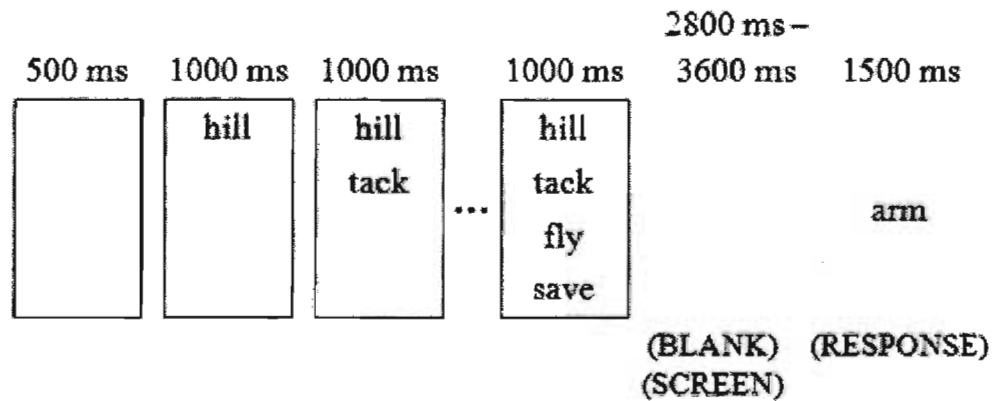


Figure 4.1

A schematic of the load Sternberg task showing a) the presentation of a four-item array and b) a graphical description of the different conditions. Italics and bold font are used to highlight condition manipulations.

a.



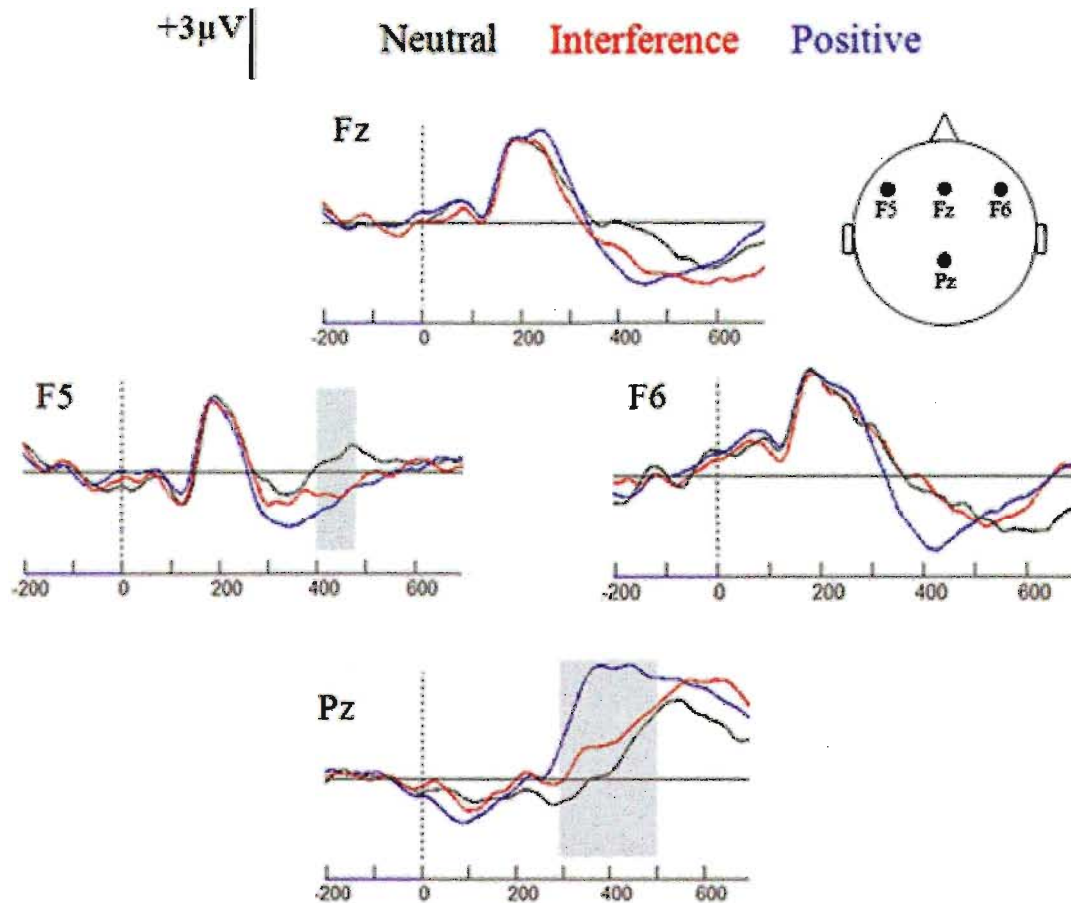
b.

Trial n-1		Trial n		Condition
jail trip <i>pine</i> art	<i>pine</i>	hill tack fly save	→ <u>if</u> tack → <u>if</u> barn → <u>if</u> art → <u>if</u> <i>pine</i>	Positive Negative Familiar Response Conflict

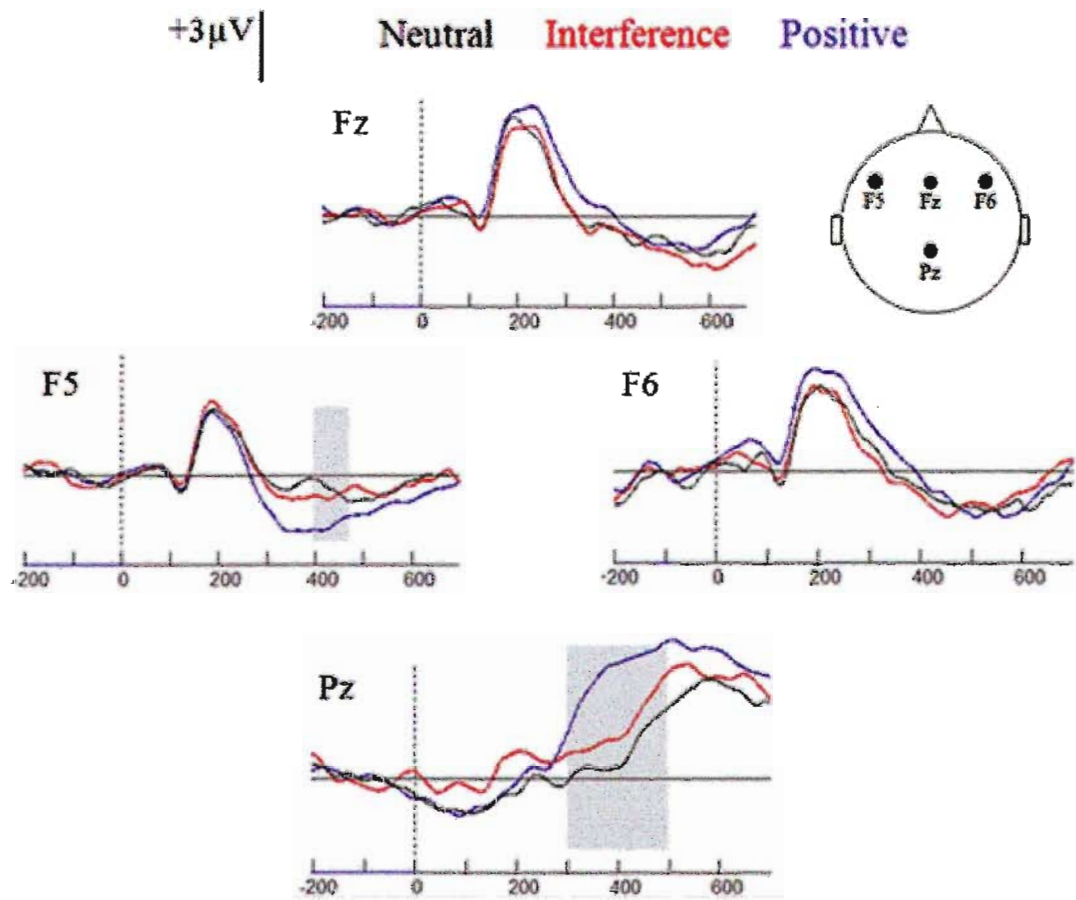
Figure 4.3

Selected channels showing the left (F5), middle (Fz), and right (F6) frontal negativities associated with the N450 and a parietal channel (Pz) showing the LPC effect at low (5a), medium (5b) and high (5c) working memory load. Positive is up and shading indicates the measured time window for each component.

a)



b)



c)

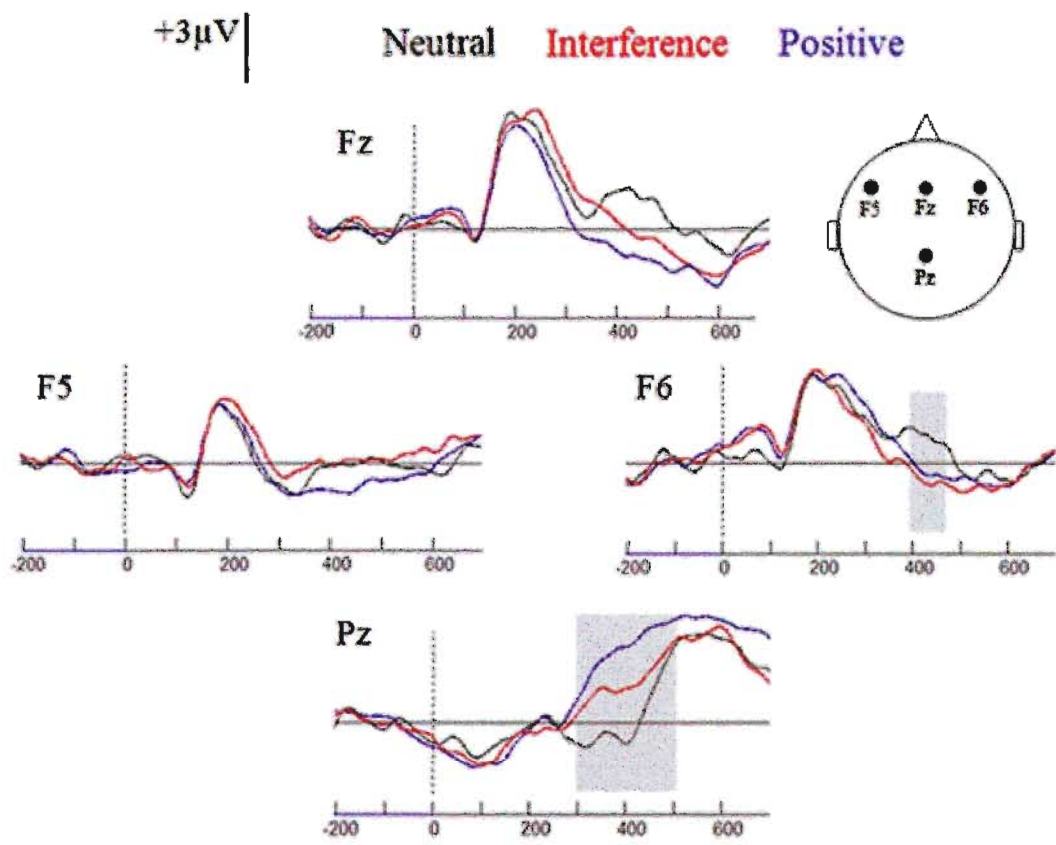
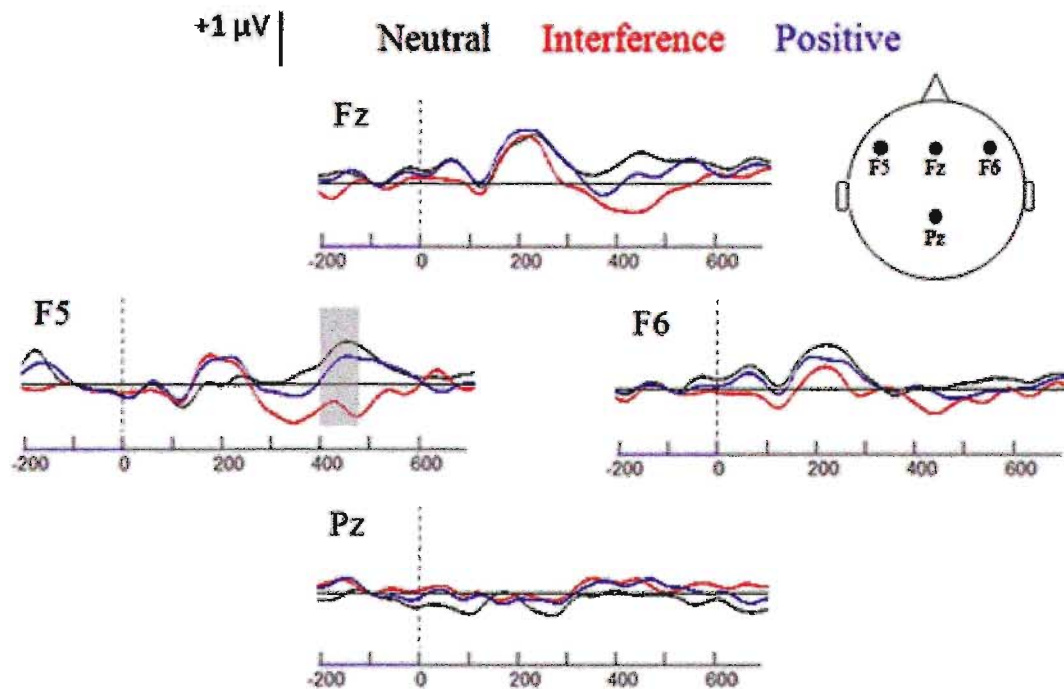


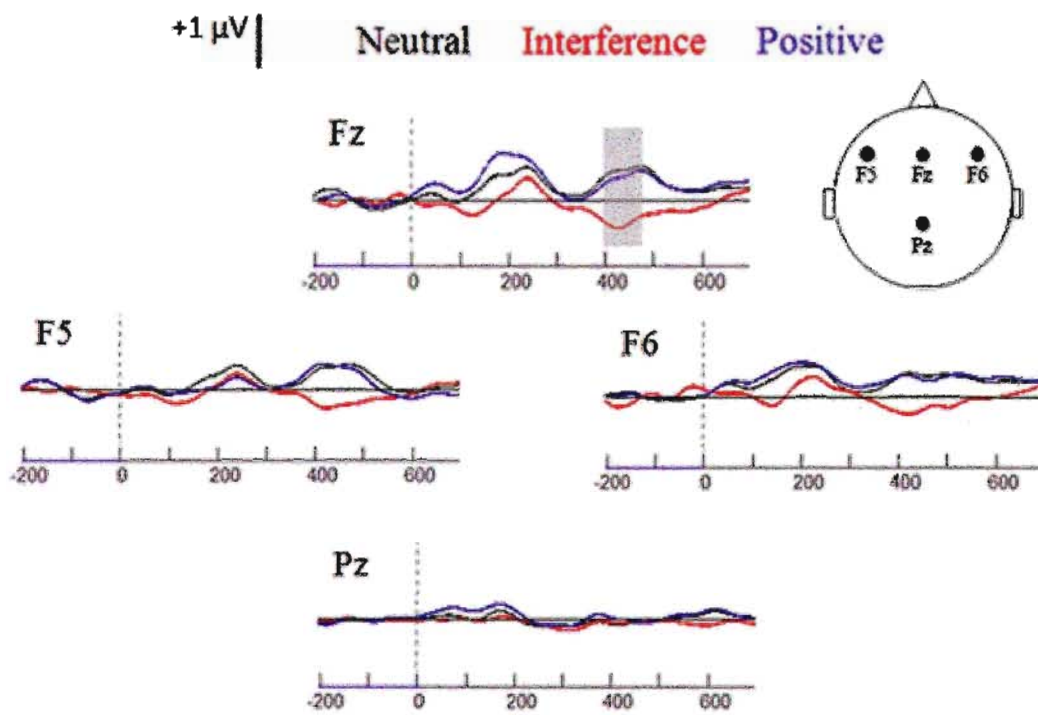
Figure 4.4

N450_{ICA} waveforms (positive up) showing the left frontal (F5), midline (AFz), and right frontal (F6) PI effect based on ICA derived data at each memory load. Note the latency differences between the peaks in the low load (peaking at approximately 460 ms) and high load (peaking at approximately 410 ms).

a)



b)



c)

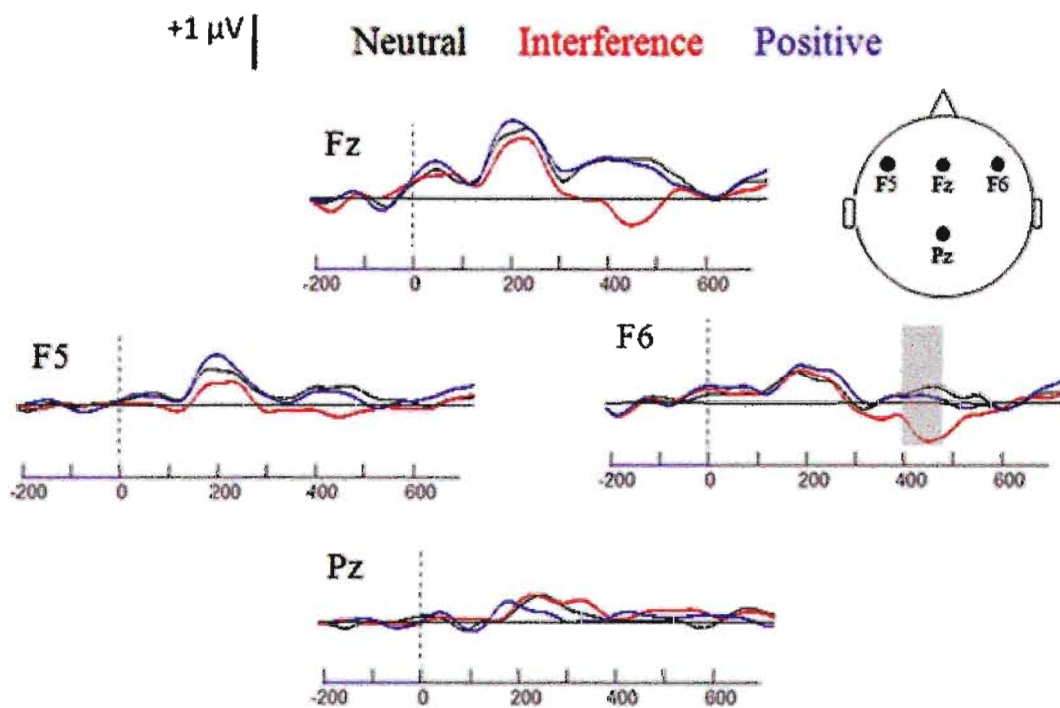


Figure 4.5

Topographies showing the PI effect (removing the Negative condition) for each of the Familiar and Response Conflict conditions at 450 ms after the probe.

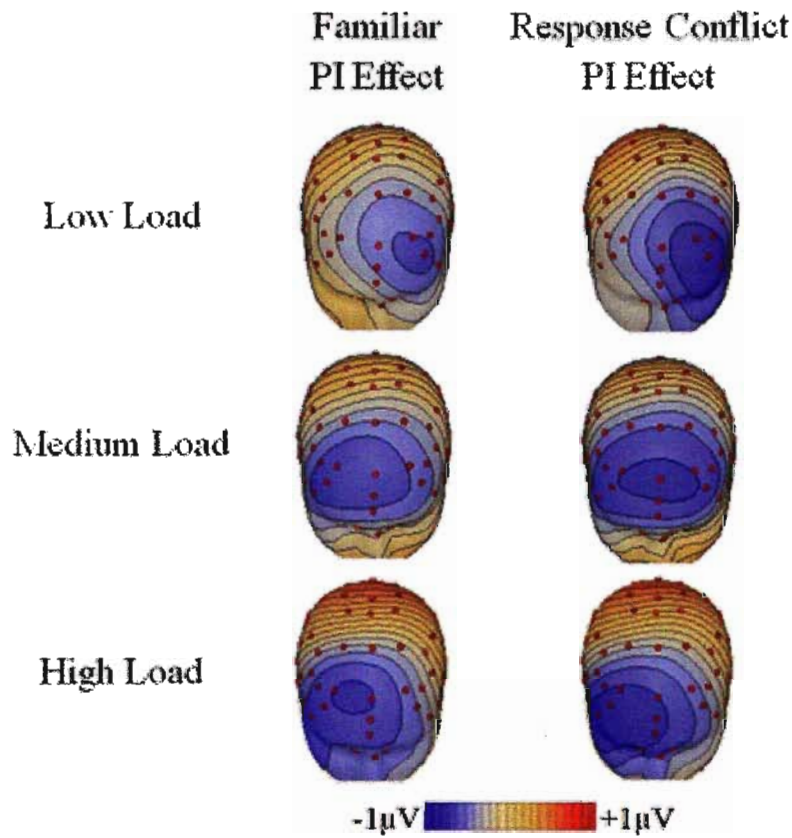


Figure 4.6

GeoSource models of neural sources of activation based on grand average difference waves (PI minus neutral) from the low and high memory loads. Crosshairs pinpoint the peak site of unique activation for each load.

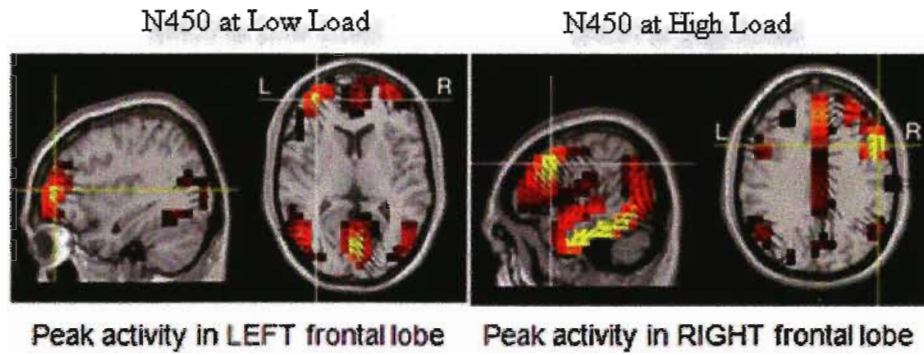
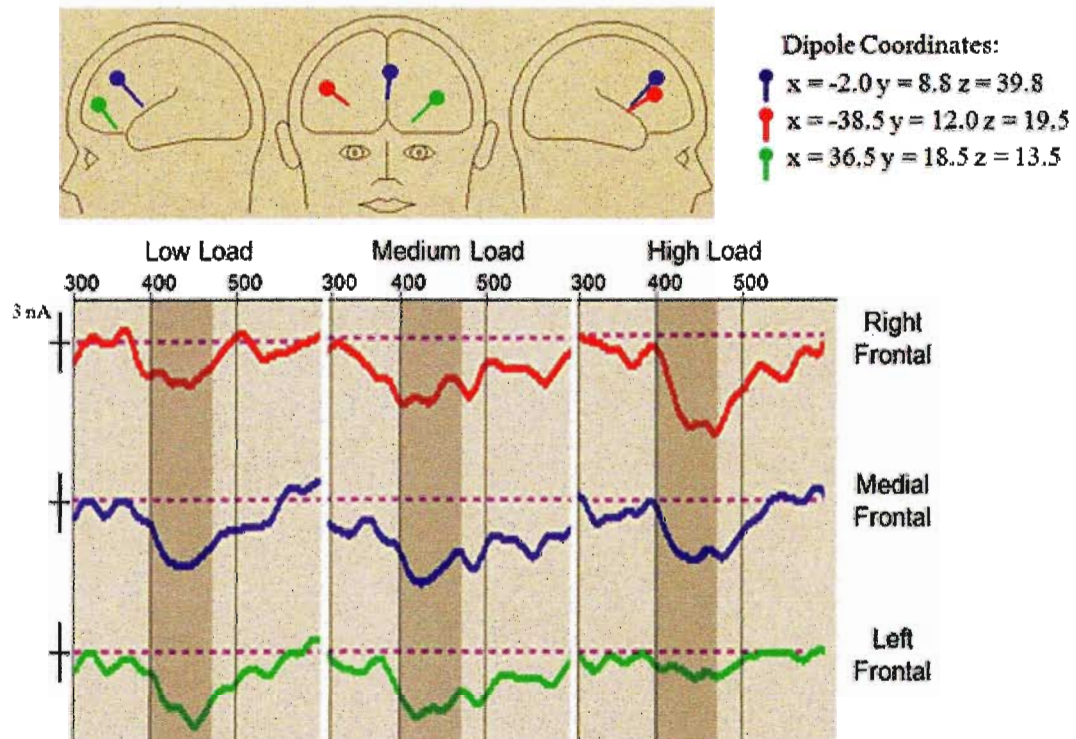


Figure 4.7

BESA model and source waveforms showing dipole activation time courses for the right frontal, left frontal, and ACC dipoles for each load.



Appendix A

Notes on Independent Component Analysis

Electrical potentials recorded at the scalp are composed of a mixed set of neural, muscular, and noise (e.g., 60 Hz) signals. By locking to an event and averaging across many trials, the strength of randomly occurring muscular and noise signals can be reduced while creating a robust measure of the average electrocortical activity to a given stimulus or event. However, the resulting average ERP component created by this method will itself be a mixture of multiple co-occurring cortical potentials, all summing at a given recording site. It is not possible to create a single correct inverse solution of latent cortical generators for a given ERP or topography based only on observations at the scalp, but it is possible to derive likely solutions that accurately explain the observed data.

Independent components analysis (ICA) is a technique based on information theory and used to create a blind separation of sources for any linear combination of latent signals based only on observed recordings of multi-channel data. The ability to decompose linearly mixed signals makes ICA useful in telecommunications, medical imaging, and digital audio/visual processing (Herault & Jutten 1986). The infomax ICA algorithm by Bell and Sejnowski (1995) integrated assumptions specific to a neural model, including an assumption that different neural networks encode independent information. Makeig et al. (1996) further adjusted the algorithm to decrease its computational burden and allow for the detection of super-Gaussian component signals having significant kurtosis in their distributions (as may be the case with reliable but rarely occurring EEG signals, such as medial frontal negativities on rare conflict trials).

A description of the ICA algorithm itself is beyond the scope of this short discussion (for an introduction to the algorithm mathematics used in the current analysis see Makeig et al., 1999). However, some important conceptual information would be useful. First, although ICA and principal component analysis (PCA) are both data decomposition strategies to separate orthogonal signals, in most cases they will produce markedly different results. This is primarily due to PCA assuming independence of latent signal strength, time-course, and topography while ICA uses higher order signal relations that allow independent signals to have non-orthogonal topographies. This is a great advantage in EEG signal decomposition because various ERP components may be independent in time and strength, yet overlap in topography.

In order to create a decomposition of time-course, signal strength, and topography, the infomax ICA algorithm uses an unguided adaptive learning process to build a model of latent components that can account for every input (i.e., EEG channel). In order to decompose the original raw data, there must be at least as many inputs (i.e. channels) as there are hypothesized independent latent signals. Furthermore, these inputs must be active for a sufficient amount of time in order to provide enough information on how the various latent signals have been mixed. A simple rule of thumb for determining if there are sufficient data to provide an ICA decomposition is that the number of time points should be at least several times the square of the number of channels. In the current study, the original 128 input channels were reduced to 64 channels to ease the computational demands and to be conservative with respect to the required number of time points for decomposition.

The process of latent component creation is iterative and begins each phase of learning by randomly selecting arrays of approximately 25 time points (containing data from all input channels). With every new array, the latent components are incrementally adjusted in order to provide a better fit to the original raw data. After an exhaustive sampling of all data arrays, the latent components are stored and the entire process is reinitiated by creating a new randomly sampled distribution of arrays but using previously stored information to aid in building a new set of latent components. Over many repetitions of this process, the amount of change or learning in the latent components reaches an asymptote as the created model begins to provide a full explanation of the input data. In the current study, the ICA decomposition was given 500 iterations to reach this learning asymptote.

The output of the ICA is a set of latent component topographies and signal strengths that, when linearly combined, reproduce all information in the original data. The topographies for the latent components are static and do not change over time but their relative contribution to any channel at any given time point is based on its signal strength (somewhat like the contribution of an electric guitar to the sound output of a rock band can be controlled by adjusting the volume control on its respective speaker). Inspecting ICA topographies and signal strengths over time can reveal which component is accounting for a given ERP. EEG_{ICA} data can then be reconstructed with any combination of independent components, included or excluded, and allowing for the removal or isolation of any observable ERP activation.