

Running head: DYNAMICS OF VISUAL WORKING MEMORY

Large-scale Network Dynamics of Visual Working Memory

by

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### Abstract

A core set of fronto-parietal brain regions is implicated in a wealth of cognitive functions. Researchers have suggested that working memory, a fundamental element in many higher-order processes, is the underlying mechanism supported by this network. However, the idea that the same fronto-parietal network underlies the qualitatively different tasks employed throughout visual working memory research is contentious. Instead, systems neuroscience has adopted the view that cognition arises out of the dynamic interaction of *several* large-scale networks. A hierarchical split divides these networks into an extrinsic system, which governs attention to the external environment, and an intrinsic system, which guides internally-directed processes. Given visual working memory involves a two-way connection between perceptual input and internal representations, the current dissertation uses converging methodologies to explore whether tasks that vary in their exogenous and endogenous attentional demands are likely supported by different network dynamics.

A quantitative meta-analysis used stress as a paradigm to investigate the differential effects of exogenous and endogenous distraction on visual working memory task performance. This analysis was followed by a controlled stress study that examined whether endogenous distraction, instigated by a psychosocial stressor, differentially influenced visual maintenance versus mental rotation. Finally, an electroencephalographic study was conducted where participants were required to store visual information despite an ongoing external distractor. Taken together, the data presented from these three studies suggest key differences between maintenance and

manipulation that may reflect the variable interplay between extrinsic and intrinsic networks. These data support the idea that the maintenance of visual information depends on right-lateralized regions of the dorsal attention network, while mental rotation recruits additional regions of the default mode and central executive networks. This work emphasizes the importance of implementing synergistic protocols while investigating cognitive function, and supports the view that the human brain consists of multiple interacting networks. It also corroborates the idea that the functional connectivity patterns accompanying cognitive state changes can impose processing constraints, and that understanding these constraints can allow us to predict behavioural impairments likely to arise in various circumstances. Similar investigations of large-scale network dynamics can provide a framework for understanding fundamental aspects of cognitive function.

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## Chapter 1: General Introduction

Working memory (WM) is the system responsible for keeping information temporarily in mind for online processing. Over the last several decades, empirical data has shaped conceptualizations of working memory systems, and a range of models have emerged (for a review, see Logie & D'Esposito, 2007). In their original model, Baddeley and Hitch (1974) characterized working memory as series of components, including both content-specific buffers for the storage of information, and control structures responsible for mediating between stored content. The original Baddeley and Hitch model was explicitly differentiated from short-term memory (Atkinson & Shiffrin, 1968) in that it allowed for the manipulation of stored information beyond its simple maintenance. In the decades following this influential model, cognitive neuroscience largely adopted a modular paradigm where cognitive functions were mapped onto specific, segregated brain regions (Meehan, 2016), and the original Baddeley and Hitch model was revised many times in attempt to more fully elucidate the storage and processing capabilities of working memory. From the confluence of psychological theory and neuroscience data, the proposal came that the prefrontal cortex is a neural substrate for working memory task functions (Goldman-Rakic, 1987; Postle, 2006). However, recent research has questioned the utility of conceptualizing cognitive processes in this way. Instead, it is becoming more apparent that cognition arises from the integrated activity of distributed networks that form fluidly and interact flexibly (Meehan, 2016; Spreng, 2012; Vossel, Geng, & Fink, 2014). There is a growing consensus supporting the view that large-scale cognitive brain networks underlie cognition, and that optimal cognitive functioning and

mental health more generally hinge on a delicate and dynamic balance between systems (e.g., Menon, 2011). Visual working memory, in particular, has more recently been conceptualized as emerging out of the dynamic interaction between large-scale cognitive networks that are involved in cognitive control, sensory perception, memory and attention (Postle, 2006; van Driel, Günseli, Meeter, & Olivers, 2017). This dissertation uses a framework centered on large-scale networks in order to investigate visual working memory. The discussion that follows reviews some of the key concepts related to these large-scale network dynamics and introduces three experimental chapters that present work conducted to evaluate this framework.

In a seminal meta-analysis, Shulman et al. (Shulman et al., 1997) uncovered a robust pattern of deactivation associated with goal-directed behaviour. This inactivity was spread across several regions now collectively called the default mode network. While this network was originally associated with task-negative and self-referential activity (Andrews-Hanna, 2012; Fox et al., 2005), it is now also thought to be recruited by other goal-directed cognitive activity, such as episodic memory (Buckner et al., 2008). The revelation that this large-scale network contains regions that consistently exhibit statistically interdependent behaviour led to discoveries of other networks in both the resting state and during goal-directed activity. These findings are shaping ideas about how endogenous and exogenous attention are manifested in the brain, which is now thought to involve several complementary processes, including bottom-up and top-down attention, as well as networks involved in sensory and memory processing.

Although terminology varies across the literature, and inclusion criteria is not always identical, two subsystems consistently emerge that support internally- and

externally-oriented cognition (Doucet et al., 2011; Hacker, Snyder, Pahwa, Corbetta, & Leuthardt, 2017; Meehan, 2016; Spreng, 2012; Zabelina & Andrews-Hanna, 2016). In one framework, these large-scale brain networks are hierarchically organized (Gleiser & Spoomaker, 2010), with a major division between two systems recently dubbed “extrinsic” vs. “intrinsic” networks (Doucet et al., 2011; Hacker et al., 2017). These two systems are dichotomous, with the extrinsic system driven by sensory stimuli and the intrinsic system directed by internal mental activity (Doucet et al., 2011). The extrinsic system, which interfaces with the external world, consists of a dorsal attention network, a ventral attention/saliency network, visual areas and somatomotor networks. The intrinsic system, which governs internally-directed processing consists of the default mode network and the fronto-parietal control network (Table 1.1).

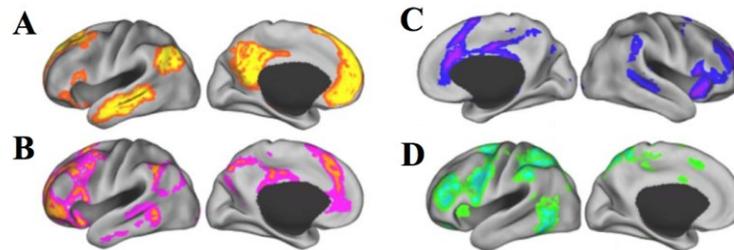


Figure 1.1: Large-scale networks implicated in higher order cognition relevant to the current dissertation. A) default mode network, B) fronto-parietal control network, C) ventral attention network, D) dorsal attention network. Modified from (Lee et al., 2012).

Table 1.1: Relevant extrinsic and intrinsic network component descriptions

Network	Subsystem	Function
Extrinsic	Dorsal attention network	Mediates top-down control of sensory networks (Corbetta & Shulman, 2002; Zabelina & Andrews-Hanna, 2016)
	Ventral attention network	Reorienting, filtering relevant interoceptive, autonomic and emotional information (Seeley et al., 2007)
Intrinsic	Default mode network	Self-referential activity and internally-directed attention (Andrews-Hanna, 2012; Fox et al., 2005)
	Fronto-parietal control network	Consists of central executive network and cingulo-opercular subsystem, involved in goal-directed behaviour (Dosenbach et al., 2006; Fedorenko et al., 2013)

Within the extrinsic system, the dorsal attention network mediates top-down control of sensory networks, and is involved in spatial attention (Corbetta & Shulman, 2002; Zabelina & Andrews-Hanna, 2016). Its core regions consist of a posterior frontal region called the frontal eye fields, and the dorsal parietal cortex (particularly the intraparietal sulcus (IPS) and superior parietal lobule) (Corbetta, Patel, & Shulman, 2008; Fox et al., 2005). The ventral attention network, on the other hand, is involved in reorienting. While this network overlaps with regions often collectively referred to as the salience network, the term “ventral attention network” will be implemented throughout the remainder of this dissertation. The ventral attention network is also implicated in filtering relevant interoceptive, autonomic and emotional information (Seeley et al., 2007). Key regions of this network include the temporoparietal junction (TPJ) and ventral frontal cortex.

Within the intrinsic system, core regions of the default mode network include the medial prefrontal cortex, posterior cingulate cortex, precuneus and the angular gyrus (Buckner, Andrews-Hanna, & Schacter, 2008; Spreng, Sepulcre, Turner, Stevens, & Schacter, 2013). In the time since its original role was suggested as mediating task-negative and self-referential activity (Andrews-Hanna, 2012; Fox et al., 2005) it has also been implicated in episodic memory (Buckner et al., 2008), autobiographical memory (Dastjerdi et al., 2011; Spreng, Mar, & Kim, 2009), semantic memory related to internal thought (Binder, Desai, Graves, & Conant, 2009), social cognitive processes (Amodio & Frith, 2006; Spreng et al., 2009), value-based decision making (Etkin, Egner, & Kalisch, 2011) and emotion regulation (Broyd et al., 2009). The fronto-parietal control network is recruited by executive control tasks (Dosenbach et al., 2006; Fedorenko et al., 2013), and is divided into the central executive and cingulo-opercular subsystems. The central

executive network is anchored in the dorsolateral prefrontal cortex, and is active across a range of tasks, especially in the context of goal-directed behaviour. For this reason, it is often associated with working memory more generally, and has been suggested to house working memory representations (Postle, 2006).

Dynamic interactions between intrinsic and extrinsic networks are suggested to facilitate the transition from internal, self-referential activity to stimulus-responsive modes primed for cognitive processing. This suggestion is bolstered by the observation that some brain regions interface with members of both intrinsic and extrinsic networks. Such regions are thought to serve as “hubs” between networks, acting as sorts of cortical mediators that direct activity according to task needs. For example, the dorsolateral prefrontal cortex couples flexibly with the dorsal attention network, as well as with default mode regions (Spreng et al., 2013). Likewise, the medial prefrontal cortex (a member of the intrinsic network) displays connectivity to both the dorsal and ventral attention subsystems (Sebastian et al., 2016). The idea of control regions that can pivot between systems is parsimonious with the tenet of “cognitive economy”, wherein brain systems save processing load and capacity by sharing resources between different tasks (Ptak, Schneider, & Fellrath, 2017; Shallice & Cooper, 2011). Indeed, this redundancy would be beneficial to the hierarchical structure of cognition wherein general-purpose functions emerge from combination of more basic processes (Ptak et al., 2017); the contributions of basic elements to more than one process would increase the brain’s overall processing power.

The interplay between external and internal attention is especially apparent in visual working memory. Visual working memory involves a two-way connection

between perceptual input and working memory representations (van Driel et al., 2017). While it is possible to attend to physically present visual stimuli, it is also possible to direct attention to visual representations in working memory. Since the inception of Baddeley and Hitch's (1974) working memory model, a "quintessence of regions" necessary for working memory have been isolated that include a set of fronto-parietal sources (Rottschy et al., 2012; Wendelken, Bunge, & Carter, 2008). However, functional specializations of these subregions as well as how they support the transition from externally-directed attention to internally-guided activity remain unclear. Furthermore, while research documents the differential recruitment of additional brain areas to this "core" working memory network during performance, it remains unclear exactly what function these additional regions perform (Lepsien & Nobre, 2006; Rottschy et al., 2012).

The inter-regional dynamics of the core working memory network have been subject to considerable debate (Wager & Smith, 2003). Hypotheses usually center on domain-specificity, whereby specific areas are suggested to fulfill specific functions (e.g., dorsolateral PFC for spatial information versus ventrolateral PFC for object information (Wilson, Scalaidhe, & Goldman-Rakic, 1993)). However, such hypotheses have been contradicted by findings that brain regions originally proposed to fulfill specific functions actually participate in multiple cognitive processes (Owen, 1997). Additionally, as mentioned, research questions the utility of strictly locationist models of brain function, and instead supports the view that cognition emerges out of the dynamic interaction of several large-scale networks. The constellation of brain regions associated with working memory overlaps considerably with other attentional networks (e.g., Shulman et al.,

2002, 2009), which has led some researchers to suggest that this core network may hold a broader role in cognition beyond working memory alone.

Incidentally, the core regions isolated in working memory research are also implicated in the putative intrinsic and extrinsic networks discussed earlier. As mentioned, accessory regions are also recruited for particular visual working memory tasks, although the exact function of these areas is unclear. For example, in addition to the “core” set of fronto-parietal regions engaged in working memory more broadly, right-lateralized regions of the dorsal attention network have been implicated during the simple maintenance of visual information, as in delayed match-to sample tasks (e.g., Jaiswal, Ray, & Slobounov, 2010; Turatto, Sandrini, & Miniussi, 2004). Left-lateralized regions of the default mode network, on the other hand, have been associated with mental rotation tasks (e.g., Lamp, Alexander, Laycock, Crewther, & Crewther, 2016; Zimmer, 2008). While the delayed match-to sample task requires the encoding and temporary maintenance of visual stimuli, mental rotation involves manipulation of an internal representation. Both tasks require an interplay between externally- and internally-directed cognition; however, this interplay is not identical. One possibility is that these tasks vary in their recruitment of large-scale network components based on differential requirements for externally and internally-directed attention.

Such variable reliance on externally versus internally-directed attention is typical within the broad range of tasks employed throughout visual working memory research. Despite Baddeley’s inclusion of a manipulation component in his original model, cognitive tasks employed to investigate working memory continue to range from those that require *only* the maintenance of information to those involving more complex

processes beyond simple maintenance, like manipulation and transformation of stored content. Thus, the library of visual working memory tasks that informs current models likely reflects a continuum of processing requirements. As pointed out by Shacter and Tulving (1994), tasks should be thought of as “probes that tap some system more than others”, rather than unequivocal indices of a single system. This advisement emphasizes the heterogeneity of visual working memory tasks, and the probability that different network dynamics underlie qualitatively different tasks.

Determining the network dynamics of a cognitive process involves the use of empirical data to infer system parameters. Unfortunately, such inverse problems are ill-posed, with typically more than one solution, or model, that can explain a given dataset. In cognitive science, particularly in those streams attempting to discover the functional organization of human cognitive processes, it is imperative that the potential set of solutions be constrained. One way to constrain this solution pool is to use converging methodologies that operate with separate reputable frameworks and to isolate viable models under these separate paradigms. If two different paradigms (consisting of separate methodologies and separate sets of empirical data) come to similar conclusions, this conclusion garners more credence. To this end, the overarching aim of the current dissertation was to use converging evidence to infer network dynamics that support maintenance and manipulation in visual working memory. It is argued that 1) visual working memory tasks vary in their internal/external attentional requirements, 2) these requirements differentially recruit intrinsic/extrinsic networks and 3) these dynamics impose cognitive constraints that can be systematically explored.

In the following chapters, three experiments are presented in which diverse approaches are implemented in order to provide converging evidence that isolates differences between maintenance and manipulation in visual working memory. In Chapter 2, a quantitative meta-analysis was conducted as a first step toward clarifying these network differences. This meta-analysis takes the unique approach of using stress as a paradigm to investigate the differential effects of internal and external distraction on visual working memory task performance. Chapter 3 describes a controlled study that institutes the framework introduced and evaluated in the meta-analysis. This experiment examines the effect of psychosocial stress on two tasks: a delayed match-to sample task and a mental rotation task. In particular, this experiment investigates how the network dynamics evoked by anxious apprehension, which interferes with top-down control of internally- directed attention, influence visual maintenance and manipulation. Chapter 4 uses electroencephalographic (EEG) methodologies to investigate the network dynamics that support visual storage in the face of external distraction. The thesis closes with an interpretation of observed results and discusses the functional significance of these findings.

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## **Chapter 2: A Meta-Analysis of Acute Stress on Visual Working Memory**

A growing body of research demonstrates a dynamic interplay between networks that support perceptual processing of external stimuli with those that support the maintenance and manipulation of internal representations (e.g., Gao et al., 2017; Meehan, 2016; van Driel, Gunseli, Meeter, & Olivers, 2017). This interplay is not identical between qualitatively different visual working memory tasks, and it is unclear how network dynamics support the transition from externally- to internally- directed cognition in specific cases. The precise nature of the large-scale network dynamics of visual working memory research is particularly difficult to assess because these networks interact differently according to contextual variables. The current chapter presents a quantitative meta-analysis that investigates how some of these contextual variables differentially influence visual working memory task performance. In particular, this analysis will demonstrate that two subtypes of stress – anxious arousal and anxious apprehension – provoke unique changes in large-scale network dynamics that differentially influence visual working memory tasks depending on specific task demands.

In response to the challenge presented by the internally-directed nature of visual working memory tasks, some researchers have used dual-task paradigms as a “psychologist’s electrode”, capitalizing on the idea that if performance on each of two tasks is lower when they are performed simultaneously (versus separately), these tasks likely rely on the same cognitive resources. There are many brain regions that display this quality of “cognitive economy”, a property wherein systems save processing load

and capacity by sharing resources between different tasks (Ptak, Schneider, & Fellrath, 2017; Shallice & Cooper, 2011). This resource sharing is not limited to task performance, but rather extends to cognitive states more generally (Zabelina & Andrews-Hanna, 2016). For instance, regions of the central executive network are functionally connected to the ventral attention network during periods of increased vigilance, but are more coupled to regions of the dorsal attention network during goal-oriented search (Meehan & Bressler, 2012; Zabelina & Andrews-Hanna, 2016). One consequence of this redundancy is that when network regions are already engaged by an ongoing cognitive state or function, they are less available to support additional processes they might otherwise facilitate. This explains why the dorsal attention network and the ventral attention network often display anti-correlated activity during cognitive task performance (Menon, 2015; Zabelina & Andrews-Hanna, 2016): when regions of the central executive network are functionally coupled to one network, they are less free to engage with another.

We can exploit this cognitive economy and resulting redundancy that occurs across both cognitive states and task performance in order to investigate cognitive architectural features of interest. In particular, this thesis is centred on the idea that several large-scale networks, which are broadly divided into extrinsic and intrinsic systems (as discussed in Chapter 1), interact flexibly with each other to participate in a range of cognitive processes. While control regions couple with extrinsic networks in order to direct attention to the external environment, they merge with intrinsic networks when attention is directed inward. These network reconfigurations occur across a range of settings, such as during threat, visual search and spatial processing on the external

side, and during memory, prospective planning and worry on the internal end. Successful task completion, and mental health more generally, hinge on a delicate and dynamic balance between systems, as evidenced by the pathologies that emerge as a consequence of aberrant network connectivity (Menon, 2011). Clinical research consistently reports systematic cognitive impairments that accompany abnormal connectivity profiles across patients (e.g., Menon, 2011; Young et al., 2016), highlighting a role for these networks in both general cognitive states and more specific cognitive functions that support task performance. We can capitalize on this dual nature to examine how cognitive states with differential external/internal processing requirements influence behavioural performance on different cognitive tasks. By exploring how connectivity changes constrain performance output, it is possible to gain a better understanding of what the actual differences are between tasks (i.e., more effectively describe the computational problem at hand), as well as the possible neural mechanisms underlying these differences.

This dissertation investigates the large-scale network dynamics that support two visual working memory tasks: maintenance (the temporary storage of visual information) and manipulation (the mental rotation of this information). Capitalizing on the principles of cognitive economy and redundancy, this first experimental section explores how cognitive states with differential external and internal processing requirements influence task performance. To this end, a quantitative meta-analysis was conducted in order to assess the influence of two anxiety subtypes on various visual tasks often employed throughout visual working memory research. This meta-analysis examined the idea that different functional connectivity patterns accompany these two anxiety subtypes, as previously suggested (and discussed below). The meta-analysis also serves as a

preliminary investigation of how the distinct cognitive states evoked by anxiety subtypes constrain two classes of visual working memory tasks that are characterized by differential external/internal processing requirements.

### **Background**

Stressful events provoke an array of behavioural and biological responses. Physiologically, stress leads to a rapid sympathetic nervous system response mediated by catecholamines, followed by the activation of the hypothalamic-pituitary-adrenal axis and the subsequent release of cortisol (de Kloet, Joëls, & Holsboer, 2005). When studied in the lab, the phenomenology of acute stress is complex and often sharply divided. While neuropsychological studies report a range of global and regional changes in neurological activity (Wendy Heller & Nitschke, 1998), behavioural studies report both improvements and impairments in cognitive function (Het, Ramlow, & Wolf, 2005a). The aim of the current meta-analysis was to explore a framework for better understanding how acute stress influences visual storage and processing performance, and to test the prediction power of this framework.

A number of plausible explanations for the discordant effects of stress on cognitive performance have been suggested (Het et al., 2005a; Lupien & McEwen, 1997; Weerda, Muehlhan, Wolf, & Thiel, 2010). Although these hypotheses explain some of the variance documented throughout the literature, they do not offer a complete account of the observed discrepancies (Het, Ramlow, & Wolf, 2005b). Part of the reason for this may be that past research has treated stress as a unitary construct instead of considering the unique phenomenological experiences introduced by different stressors. Instead of prompting a singular, discrete reaction, research suggests the stress response is actually

composed of two distinct types of anxiety that differ in psychological, neurological and physiological characteristics (Engels et al., 2007a; J. B. Nitschke, Heller, Palmieri, & Miller, 1999; Shackman et al., 2006a; Vytal, Cornwell, Arkin, & Grillon, 2012). Anxious arousal is associated with a threat-induced autonomic somatic response typical of flight or fight, and is distinguished by physical symptoms of physiological hyper-arousal and somatic tension, including changes in heart rate, skin temperature and electromyographic activity (Barlow, 1991; Heller, Nitschke, Etienne, & Miller, 1997). Anxious apprehension, in contrast, is distinct from arousal and provokes symptoms of a more cognitive nature, including sub-vocal worry and rumination, especially of future events (Heller et al., 1997; Lin, Moran, Schroder, & Moser, 2015; Nitschke, Heller, Imig, McDonald, & Miller, 2001; Nitschke et al., 1999).

Research suggests that many cognitive states, including those associated with certain psychopathologies (Menon, 2011), are associated with dynamic changes in several large-scale networks - networks that form fluidly and interact flexibly (Burdwood et al., 2016; Meehan, 2016; Spreng, 2012; Vossel, Geng, & Fink, 2014). As discussed previously (Chapter 1), a main hierarchical division splits these large-scale networks into “extrinsic” and “intrinsic” systems. The extrinsic network interfaces with the external world, while the intrinsic network directs attention and processing toward internal representations (Doucet et al., 2011; Hacker, Snyder, Pahwa, Corbetta, & Leuthardt, 2017; Zabelina & Andrews-Hanna, 2016). This hierarchical division between extrinsic and intrinsic networks is particularly relevant to research investigating stress effects on cognitive function given the nature of arousal and apprehension. While arousal imposes a state of heightened vigilance and externally-directed attention, apprehension seems to

cause increased internally-focused behavior. Given this distinction, a consideration of extrinsic/intrinsic network dynamics associated with various stressors is prudent.

Although terminology varies across research groups, and inclusion criteria is not always identical, several key networks have consistently emerged as supporting extrinsic versus intrinsic processes (Zabelina & Andrews-Hanna, 2016). To review, the dorsal attention network, which enables top-down control of attention to visual stimuli and spatial location (Corbetta, Patel, & Shulman, 2008), belongs to the broader extrinsic network. The default mode network, on the other hand, which is engaged during perceptual-independent cognition (Spreng, 2012), such as during self-referential thought or when operations are performed on internal representations of perceptual stimuli (Andrews-Hanna, Smallwood, & Spreng, 2014), is part of the intrinsic system. While these networks facilitate external and internal attention, they are influenced by the ventral attention network (which overlaps with regions of the salience network, as previously mentioned) and frontoparietal control network (which consists of central executive and cingulo-opercular networks). Although the ventral attention and frontoparietal control networks primarily participate in extrinsic and intrinsic network activity, respectively, they are recognized as important hubs that can act as switches between systems (Doucet et al., 2011; Hacker et al., 2017; Power, Schlaggar, Lessov-Schlaggar, & Petersen, 2013; Zabelina & Andrews-Hanna, 2016). For example, the ventral attention network has been suggested to act as a circuit breaker for the dorsal attention network (Corbetta & Shulman, 2002; Vossel et al., 2014; Young et al., 2016). Functionally, the consequences of this circuit breaking include interference with top-down signals for attention to objects or features, maintenance of attentional sets in memory and response or action selection

(Corbetta & Shulman, 2002; Dolcos & McCarthy, 2006; Vossel et al., 2014). The frontoparietal control network, in particular its executive subsystem, which is anti-correlated with regions of the default-mode network in healthy individuals during rest (Andrews-Hanna et al., 2014; Fox et al., 2005), plays an important role in placing deliberate constraints on thought (Christoff, Irving, Fox, Spreng, & Andrews-Hanna, 2016). When the frontoparietal network fails to exert top-down control on internally-directed processes, and functional connectivity increases within the default mode network, the result is unconstrained thought flow (Christoff et al., 2016).

The dynamic interaction of the extrinsic and intrinsic networks imposes specific cognitive constraints depending on which subsystems are engaged. The network configurations that accompany arousal and apprehension can therefore be used as a starting point to consider what differential constraints might exist in both cases, and to predict how these constraints influence behavioural performance. In the case of anxious arousal, activation increases in the ventral attention/salience network: as locus coeruleus activity and noradrenaline increase (particularly to the right hemisphere), activity increases in the right anterior insula, (Abboud et al., 2006; Corbetta & Shulman, 2002; Critchley, 2009; Etkin & Wager, 2007; Fisher et al., 2014; Menon, 2011; Meyer, Strittmatter, Fischer, Georg, & Schmitz, 2004) and functional connectivity increases between areas of the ventral attention network (i.e., between the temporoparietal junction (TPJ) and surrounding regions of the temporoparietal and occipital cortices (Greene & Soto, 2014)). When these regions of the ventral attention network are engaged during anxious arousal (McMenamin, Langeslag, Sirbu, Padmala, & Pessoa, 2014), or during the bottom-up capture of attention by salient stimuli, functional connectivity is disrupted

within the dorsal attention network. Connections are decreased between the intraparietal sulcus and right frontoparietal regions (including the superior frontal gyrus and right posterior parietal cortex (Greene & Soto, 2014)), and between the right anterior cingulate and regions of dorsal attention and central executive networks (including the right dorsolateral prefrontal cortex and right posterior parietal cortex in particular (McMenamin et al., 2014; Sridharan et al., 2008)). Interestingly, the right dorsolateral prefrontal cortex has also recently been suggested to play a role in regulation of ventral attention network activity based on the clinical observation that chronic hypoactivity in this region leads to over activity of the ventral attention network. These changing dynamics result in an automatic interference with attentional control to external stimuli and impaired goal-directed attention. This inefficient filtering leads to attentional spillover to the peripheral visual field (Rossi & Pourtois, 2014) and to previously unattended or neutral visual information (Hermans et al., 2011; Rossi & Pourtois, 2014), resulting in disengagement from ongoing task sets, distractibility and hypervigilance (Valentino & Van Bockstaele, 2008). Based on this altered network configuration, anxious arousal invokes a state of threat-induced hyper-orienting and lowers the threshold for distractors to gain access to task-relevant neural resources (Young et al., 2016). Given these facts, it is likely that anxious arousal impairs cognitive processes that rely on dorsal attention regions, in particular, the right dorsolateral prefrontal cortex and the right posterior parietal cortex. Such processes include: short-term maintenance of visual information, visual search and attention to objects or features (Corbetta & Shulman, 2002; Vossel et al., 2014), location memory (Wen, Yao, Liu, & Ding, 2012)

and tasks involving reordering, such as reverse spatial span (Koenigs, Barbey, Postle, & Grafman, 2009) (See Table 2.3 for results of narrative review).

Whereas anxious arousal results in the reallocation of neural resources away from dorsally located attention networks and impairs top-down attention to external stimuli, anxious apprehension shifts activity to regions of the default mode network. In healthy individuals during rest, the default mode and the central executive subsystem are anti-correlated (Andrews-Hanna et al., 2014; Fox et al., 2005); however, during anxious apprehension, the default mode network is less-suppressed, and task-related central executive activity declines. Connectivity not only increases within regions of the default mode network, including the medial prefrontal cortex, posterior cingulate cortex and posterior parietal cortex, particularly the left inferior parietal lobule (Luo, Kong, Qi, You, & Huang, 2016), but also *between* areas of the default mode network and regions of the central executive network (Bijsterbosch, Smith, Forster, John, & Bishop, 2014; Rossi & Pourtois, 2014). The result is a reallocation of executive resources away from task-relevant processing and toward unconstrained, internally-directed thought (Qin, Hermans, van Marle, Luo, & Fernández, 2009). This shift in functional connectivity during cognitive or psychological stress is suggested to relate to the down-regulation of negative emotion associated with sub-vocal worry and rumination (Bijsterbosch et al., 2014; Rossi & Pourtois, 2014). As top-down control is shifted toward the maintenance of self-referential thought, the executive resources supporting apprehension-related activity are no longer available to support ongoing activities requiring attentional control. In particular, the left dorsolateral prefrontal cortex (Bishop, Duncan, Brett, & Lawrence, 2004; Disner, Beevers, Haigh, & Beck, 2011; McRae et al., 2010; Vaisvaser et al., 2016;

Wang et al., 2015) and the left inferior parietal lobe (Luo et al., 2016; McRae et al., 2010), which are involved in emotion regulation and processing, become less available to support working memory related activity (e.g., (Wang et al., 2015)). Based on these dynamics, it is likely that anxious apprehension provokes impairment on tasks that are supported by overlapping on regions of the central executive subsystem, as well on tasks observed to couple this activity with default mode network activity, as when operations are performed on internal representations (e.g., mental rotation (Gao et al., 2017)).

The notion that anxious apprehension and anxious arousal impair tasks that rely predominantly on left- and right-hemispheric support, respectively, is not new (Engels et al., 2007b; Heller et al., 1997; Nitschke, 1998; Shackman et al., 2006b). The bulk of this research, however, has explained resulting impairments (or lack thereof) by assuming generalized competition between anxiety and cognitive task performance for the same brain regions. This has led to the broad conceptualization that anxious apprehension impairs verbal working memory whereas anxious arousal impairs spatial attention (e.g., Vytal, Cornwell, Letkiewicz, Arkin, & Grillon, 2013). This framework, however, does not explain a number of results that document impairing effects of apprehension on spatial attention or of arousal on verbal working memory (Elzinga, Bakker, & Bremner, 2005; Schoofs, Wolf, & Smeets, 2009). This framework also fails to address the possibility that network dynamics ideal for one visual working memory task (e.g., maintenance), might not be optimal for another (e.g., manipulation). The current paper therefore aimed to contribute to the literature by: re-operationalizing acute stress as either anxious arousal or anxious apprehension; performing a narrative review to confirm the functional connectivity changes believed to occur in each case; and predicting how these

changes affect various tasks employed in visual working memory research – tasks that vary in their external and internal attentional requirements. With respect to the latter aim, tasks were broadly characterized as two types: storage (meant to reflect an increased relative external attention requirement) and manipulation (meant to reflect an increased relative internal attention requirement). It is important to note that, while these classes were constructed in order to capture a major qualitative difference between task types often employed throughout the visual working memory literature, I do not suggest that these tasks are pure indices of storage or manipulation; rather, I adopt the view taken previously that tasks should be thought of as probes that tap some systems more than others, rather than unequivocal indices of a single system (Schacter & Tulving, 1994). For example, while care was taken to select manipulation tasks that do not require a heavy storage load, it is acknowledged that these tasks are not free from maintenance requirements, but rather reflect a relatively lower maintenance demand when compared to storage tasks.

The primary goal of the current meta-analysis was to determine whether a consideration of functional connectivity changes brought on by arousal (via reallocation from dorsal attention networks to ventral attention networks) and apprehension (via reallocation of resources to default mode pathways) can help to explain the varied influence of stress on visual tasks that has traditionally been observed. Another aim of this analysis was to investigate the idea that visual tasks vary in external versus internal attentional requirements such that the network dynamics that facilitate one task are not necessarily optimal for another. In particular, a double dissociation effect of stress on visual task performance was predicted, such that arousal, presumed to alter extrinsic

system activity, was predicted to impair performance on storage but not manipulation tasks, while apprehension, presumed to influence intrinsic system activity, was predicted to impair manipulation but not storage tasks.

	<b>AROUSAL</b>	<b>APPREHENSION</b>
<b>STORAGE (External attention)</b>	<b>IMPAIRMENT</b>	<b>NO IMPAIRMENT</b>
<b>MANIPULATION (Internal attention)</b>	<b>NO IMPAIRMENT</b>	<b>IMPAIRMENT</b>

Figure 2.1: Predicted double dissociation effect of stress subtypes on storage and manipulation tasks.

## **Methods**

### **Overall Sample of studies**

Studies for the meta-analysis were obtained by searching online databases (PsychINFO, Scopus, Web of Science, PubMed, Dissertations and Theses Fulltext). Permutations of the following truncated key words were crossed in order to retrieve studies using eligible stress induction paradigms and visual tasks: anxiety, arousal, apprehension, cortisol, manipulation, memory, processing, rotation, search, spatial, storage, stress, tracking, visual. The search included all studies published through November 2016 and yielded 4023 initial hits. Abstracts for each hit were reviewed, and those studies that could not be excluded based on the selection criteria were retrieved for further inspection. The reference sections for each retrieved hit were also searched for relevant papers. See Table 2.1 for a list of study characteristics.

**Study selection criteria**

Studies were restricted to those that: a) were peer reviewed; b) involved human participants; c) included a sample of healthy participants aged 18-45 with no known visual, neurological or psychological impairments; d) collected data from awake individuals during the day; and f) included sufficient statistical information to calculate effect size  $g_{\text{hedges}}$  and its variance.

**Stress induction selection criteria**

Studies were retained for analysis if they compared two conditions—acute stress vs. control—where the stress condition consisted of a mild physical, psychological or pharmacological stressor (Dhabhar, 2008). Stress induction was required to elicit an enduring stress effect as demonstrated through significantly elevated levels of cortisol or a minimum of two other measures associated with stress (e.g., subjective measures and physiological measures). Given the nature of the current analysis, in that it examined visual tasks characterized by a large degree of heterogeneity, in addition to a range of different stressors, an attempt was made to reduce further variability by including only acute (i.e., short-lived) laboratory stressors. These criteria excluded: extended and chronic stressors (e.g., burnout) where individuals had no indication of when the stress might terminate; studies examining performance differences in trait-associated anxiety (as advised by Shackman et al., 2006a) and studies administering cortisol over prolonged periods (e.g., Young, Sahakian, Robbins, & Cowen, 1999). Stressors that elicited cortisol levels above that typically seen with moderate lab stressors (e.g., Kirschbaum, Wolf, May, Wippich, & Hellhammer, 1996) or that employed extreme or unnatural levels of physical stress (e.g., firefighting simulation (Robinson, Leach, Owen-Lynch, & Sünram-

Lea, 2013)) were also excluded from analysis. This decision was made in order to limit any potential influence of physical fatigue on glucose metabolism, which might otherwise confound effects. Emotion induction paradigms (e.g., presentation of aversive pictures) were also excluded given emotion and stress are induced in different ways and influence cognition differently (Zhao, Lynch, & Chen, 2010).

Stress induction paradigms were also categorized based on a narrative review (Table 2.2) according to whether they were predominantly physical stressors, predicted to elicit anxious arousal, or cognitive stressors, predicted to induce anxious apprehension. Examples of physical stressors include cortisol administration, which has been shown to increase right-frontal EEG activity (Tops et al., 2005), as well as the Cold Stress Task, a peripheral noradrenergic system activator (e.g., (Ishizuka, Hillier, & Beversdorf, 2007). Examples of cognitive stressors include the Trier Social Stress Task (TSST) and the Public Speaking Task both believed to elicit anxious apprehension and to demonstrate a significant increase in cortisol levels (Hoffman & al'Absi, 2004; Schwabe, Haddad, & Schachinger, 2008). Stressor descriptions as well as support for their classification appear below (See Table 2.2 for results of narrative review). Induction paradigms that included elements of both physical and cognitive stressors, which were suspected of inducing both anxious apprehension and anxious arousal, were categorized as both stressor types (physical and cognitive) unless a case could be made that the stressor primarily induced one subtype of anxiety over the other. When studies included data for more than one dose of corticosteroid administration, the higher of the two doses was selected for analysis. When data were presented for subsets of participants who

Table 2.1: Descriptive features and average effect sizes for included studies

Study	n	Stress paradigm	Anxiety Subtype	Visual task	Visual task category	Outcomes Analyzed	Predicted Competitor	Effect Size (g)
Beckner, 2010	35	TSST	Cog.	Film Task	Maint.	% accuracy	Arousal	-0.071
Bogdanov & Schwabe, 2016	38	TSST	Cog.	Backward Corsi	Reord.	Max span	Arousal	-0.269
Breitberg et al., 2013	22	Cortisol Admin.	Phys.	Spatial Span Task	Maint.	Mean span	Arousal	-0.076
Cain, Dunsmoor, LaBar, & Mitroff, 2001	12	Threat of shock	Phys.	Baggage search	Maint.	Miss rate high salience single Miss rate low salience dual Miss rate low salience single	Arousal	-0.023
Clarke & Johnstone, 2013	18	Threat of shock	Phys.	N-back visual task	Maint.	Percent correct low load Percent correct high load	Arousal	-0.178
Cornwell, Arkin, Overstreet, Carver, & Grillon, 2012	25	Threat of shock	Phys.	Virtual Navigation Morris Water Task (hidden and visible)	Way finding Cue following	Heading error	Appr. Arousal	0.352 0.038
Delahaye et al., 2015	29	TSST	Cog.	Memory labyrinth	Way finding	Accuracy	Appr.	-0.726
Duncko, Cornwell, Cui, Merikangas, & Grillon, 2007	28	Cold stress task	Phys.	Virtual Navigation Morris Water Task (hidden platform)	Way-finding	Heading error; path length	Appr.	0.709
Elzinga, Bakker, & Bremner, 2005	16	Cognitive challenge task	Cog.	Reverse Walk Task	Rotation	Number correct	Appr.	-0.199
Gabriel, Hong, Chandra, Lonborg, & Barkley, 2011	151	Cold stress task	Phys.	Mental Rotation Cue Isolation Task	Rotation Maint.	Accuracy (% correct); RT Distal gradient accuracy; proximal gradient accuracy; RT	Appr. Arousal	0.213 -0.038
Graver & White, 2007	11	Modified TSST	Cog.	Spatial span forward Spatial span backward	Maint. Reord.	Maximum span	Arousal Arousal	0.449 0.369
Guenzel, Wolf, & Schwabe, 2014a	59	Cortisol Admin.	Phys.	Spatial navigation task S-R navigation task	Way finding Cue following	Errors; time	Appr. Arousal	0.382 0.268
Guenzel, Wolf, & Schwabe, 2014b	63	SECPT	Both	Spatial navigation task S-R navigation task	Way finding Cue following	Errors; number didn't reach learning; time	Appr. Arousal	0.342 -0.364

Hoffman & Al'Absi, 2004	25	Public speaking task	Cog.	Memory Span Forward Memory Span Backward	Maint. Reord.	Forward span Backward span	Arousal Arousal	0.028 -0.106
Iwasaki, 2012	44	TSST	Cog.	Multiple Object Tracking Task	Tracking	Accuracy rate middle responders Accuracy rate high responders	Arousal	0.297
Janelle, 1997	16	Time to event paradigm	Both	Central Driving Task	Tracking	Major driving errors; Lap speed	Arousal	0.364
Klopp, Garcia, Schulman, Ward, & Tartar, 2012	50	TSST	Cog.	Virtual Navigation Morris Water Task (hidden platform)	Way-finding	Latency to reach platform; path length; heading errors	Appr.	-0.032
Kuhlmann & Wolf, 2006	29	Cortisol Admin	Phys.	Picture Memory Task (neutral pictures)	Maint.	Free recall	Arousal	-0.060
Lai et al., 2012	11	TSST & Cold pressor	Both	Sternberg Complex Visual Scene Task	Maint.	Correct rejection accuracy; Hit rate accuracy; RT for both	Arousal	0.288
Lavric, Rippon & Gray, 2003	36	Threat of Shock	Phys.	N-back visual task	Maint.	Accuracy; RT	Arousal	-0.366
Luethi, Meier, & Sandi, 2009	35	TSST	Cog.	Map Learning Spatial Task	Maint.	Free recall	Arousal	0.678
Mahoney, Castellani, Kramer, Young, & Lieberman, 2007	19	Cold Pressor	Phys.	Match-to Sample 4-Choice Reaction Time Task	Maint. Visual search	Correct responses Total errors	Arousal Arousal	-0.833 -0.967
Newcomer et al., 1999	51	Cortisol Admin	Phys.	Delayed match-to sample Spatial delayed response task (5s delay, 120 s delay)	Maint.	Accuracy; Error (for both)	Arousal Arousal	-0.205
Olver, Pinney, Maruff, & Norman, 2015	23	TSST	Cog.	N-back visual task	Maint.	RT	Arousal	-0.203
Pariante et al., 2012	20	Cortisol Admin.	Phys.	Modified spatial WM task	Maint.	Between search errors; within search errors;	Arousal	-0.345
Richardson & Tomasulo, 2011	46	Star Mirror Tracing Task	Cog.	Perspective taking task Virtual Navigation task (combined hidden platform and visible platform)	Rotation Combined Way-finding & Cue-following	Reaction time for error Pointing errors, RT; Virtual errors; RT	Appr. Both	-0.395 0.002
Russell, 2013	49	Threat of shock	Phys.	RVIP	Visual search	Accuracy; RT	Arousal	-0.095
Schwabe, Haddad, & Schachinger, 2008	84	Cortisol Admin.	Phys.	3D Model Room Task	Way-finding Cue-following	Spatial strategy Stimulus-response strategy	Appr. Arousal	0.616 -0.616
Shackman et al., 2006	55	Threat of	Phys.	N-Back Visual Task	Maint.	Reaction time; Mean transformed	Arousal	-0.307

Stauble, Thompson, & Morgan, 2013	33	Shock TSST	Cog.	Change detection	Maint.	accuracy Number objects retained	Arousal	0.297
Thomas, Laurance, Nadel, & Jacobs, 2010	29	TSST	Cog.	Spatial navigation task	Way- finding Cue- following	Time to find target invisible trials Time to find target visible trials	Appr. Arousal	-0.873 -0.279
Vaz, Pradella-Hallinan, Bueno, & Pompéia, 2011	20	Cortisol Admin.	Phys.	Trail making Part A Corsi block backward Corsi block forward	Visual search Reord. Maint.	Reaction time Number correct Number correct	Arousal Arousal Arousal	0.040 -0.220 -0.536
Weerda, Muehlan, Wolf, & Thiel, 2010	41	TSST	Cog.	Spatial Recognition	Maint.	Accuracy; RT	Arousal	0.029
Wraga, Helt, Jacobs, & Sullivan, 2007	30	Negative stereotype task	Appr	Mental rotation	Rotation	Errors	Appr.	-0.807
Zhang, 2016	8	Social evaluative threat paradigm	Cog.	Raven's Progressive Matrices Corsi task	Spatial reasoning Maint.	Z score Span length	Appr. Arousal	-0.552 0.160

Note: Appr. = Apprehension, Cog. = Cognitive, Maint. = Maintenance, Phys. = Physical, Reord. = Reordering, RT = Reaction time, SECPT = Socially Evaluated Cold Pressor Task, TSST = Trier Social Stress Task

exhibited only a marginal response, effect sizes were calculated for high-responding group only. These criteria were instituted in order to increase the likelihood that the current analysis included samples where a robust physical or cognitive stress response was indeed elicited.

Table 2.2: Stress induction paradigms for all included studies

Stress Induction	Description	Support
<b>Physical (Arousal)</b>		
Cold pressor	Participant immerses hand into ice water, typically for one minute (Hines & Brown, 1933)	Lateralized activity increase in: right insula, right cingulate and cerebellar cortex (Harper et al., 2003); right DLPFC (Graff-Guerrero et al., 2005)
Pharmacological	Drug administration. Participant receives either placebo or drug designed to increase stress hormone	Increased activity and interconnectivity of key VAN areas (Cole et al., 2013; Hermans et al., 2011; Onur et al., 2009)
Threat of Shock	Participant anticipates delivery of a small electric shock	Increased VAN activity (Klumpers et al., 2015; McMenamin, Langeslag, Sirbu, Padmala, & Pessoa, 2014)
<b>Cognitive (Apprehension)</b>		
	Paradigms designed to increase apprehension or worry, including: Cognitive challenge task, mirror tracing task, public speaking task, star mirror tracing task, time to event, trier social stress task	Increased activity within: DMN (Luo, Kong, Qi, You, & Huang, 2016); CEN, particularly left DLPFC (Quaedflieg et al., 2015; Vaisvaser et al., 2016) and left inferior parietal lobe (Luo et al., 2016). Increased activity between areas of the DMN and CEN (Bijsterbosch, Smith, Forster, John, & Bishop, 2014).
<b>Both</b>		
	Time-to event task and anxiety producing instructional sets. Sequence of sessions leading up to competitive event paired with directives designed to increase competition saliency.	Increased levels of cognitive anxiety and physical stress as indexed by the Cognitive State Anxiety Inventory (Janelle, 1997).
	Socially evaluated cold pressor task. Cold pressor task paired with modified or traditional Trier Social Stress Task	See above.

Note: CEN = Central executive network, DMN = Default mode network, DLPFC = dorsolateral prefrontal cortex, VN = Ventral attention network

Table 2.3: Visual task classifications

Category	Description	Included Tasks	Brain Activity	Predicted Competitor
Maint.	Participant retains visual material across short delay and immediately attempts recall	Change detection task, Corsi block forward, Film task, Match-to sample, Memory span forward, Modified spatial working memory task, N-back visual task Picture memory, Spatial span forward, Sternberg complex visual scene task	Increased activation in: right DLPFC (Jaiswal, Ray, & Slobounov, 2010; Turatto, Sandrini, & Miniussi, 2004); right posterior parietal cortex (Turatto et al., 2004); a right lateralized dorsal pathway including dorsal PFC and parietal-occipital cortex (Ventre-Dominey et al., 2005). Deactivation of right TPJ associated with increased performance (Anticevic, Repovs, Shulman, & Barch, 2010).	Arousal
Visual Search	Participant actively scans visual environment for target	Baggage search, Cue isolation task, Map search task, Rapid visual information processing task, Telephone search task, Trail making Part A	Deactivation of ventral network, especially right TPJ, correlated with improved performance (Corbetta, Patel, & Shulman, 2008; Vossel, Geng, & Fink, 2014)	Arousal
Tracking	Stationary participant uses visual information to follow moving object	Central driving task, Multiple object tracking	Supported by dorsal attention network (Alnaes et al., 2014)	Arousal
Cue Following	Participant navigates to visible target	Map learning task, Morris Water Maze visible platform, Spatial navigation task (visible trials) Stimulus-response navigation task	Supported by right lateralized network including right anterior PFC (Hartley, Maguire, Spiers, & Burgess, 2003) and right parietal lobe (Rodriguez, 2010)	Arousal
Way-Finding	Participant navigates to non-visible target in a familiar environment from different starting points	Memory labyrinth, Morris Water Maze hidden platform, Spatial navigation (invisible trials), 3D model room task	Beyond hippocampal network, the following are activated: IPL (Rauchs et al., 2008), especially left ( Böhner et al., 2015, Wagner, Shannon, Kahn, & Buckner, 2005), left frontal cortex ( Böhner et al., 2015; Cabeza & Nyberg, 2000; Konishi, Wheeler, Donaldson, & Buckner, 2000). Morris water maze hidden platform trials (but not visible	Appr.

Reord.	Participant re-orders serially presented stimulus immediately after presentation	Corsi Block backward, Memory span backward, Spatial span backward, Reverse walk task	trials) correlate with mental rotation performance (Astur, Tropp, Sava, Constable, & Markus, 2004) Increased activation in: right DLPFC (Crone, Wendelken, Donohue, van Leijenhorst, & Bunge, 2006; Trumbo et al., 2016); right superior parietal lobe (Champod & Petrides, 2007; Koenigs, Barbey, Postle, & Grafman, 2009)	Arousal
Rotation	Participant rotates a mental representation of a visual stimulus by a predetermined angular distance	Barn task, Mental rotation task, Perspective taking task, Reverse walk task	Increased activity in: left IPL, left fusiform gyrus (Lamp, Alexander, Laycock, Crewther, & Crewther, 2016); left IPS (Alivisatos & Petrides, 1997; Petrides, Alivisatos, Evans, & Meyer, 1993); left PPC (Wolbers, Schoell, & Büchel, 2006); left inferior frontal gyrus, right superior frontal gyrus, right precuneus (Gao et al., 2017). General imagery increases activity in left temporal cortex and left IPS (Zimmer, 2008)	Appr.
Spatial-relations Reasoning	Participant views several geometric designs and must determine the spatial pattern that exist amongst them	Raven's progressive matrices	Increased activity in left anterior DLPFC (Kroger et al., 2002)	Appr.

Note: Appr. = apprehension, DLPFC = dorsolateral prefrontal cortex, IPL = inferior parietal lobule, IPS = intraparietal sulcus, Main. = maintenance, Reord. = reordering, PPC = posterior parietal cortex

### Visual task selection criteria

The utility of the present meta-analysis came from considering how both stress induction methodologies and visual tasks used throughout the visual working memory literature engage neural circuitry, and examining how performance is affected when neural circuitry overlaps. In an attempt to fully represent the spectrum of tasks typically used in visual working memory research, while maintaining a reasonable degree of homogeneity, a specific range of studies were eligible for inclusion based on predicted neural involvement. Eligible tasks fell into one of eight possible categories:

maintenance, visual search, tracking, cue-following, way-finding, reordering, manipulation (mental rotation) and spatial relations reasoning (Table 2.1, Table 2.3). Because key brain areas of the dorsal attention, default mode, ventral attention and frontoparietal networks differentially support these visual tasks, I predicted that the functional connectivity changes accompanying physical and cognitive stressors would compete with task performance in different ways. In order to examine whether this competition explained some of the variance surrounding stress and visual task performance, the tasks included were coded according to whether they were predicted to experience competition with physical or cognitive stress paradigms (Table 2.3).

Tasks excluded from analysis included those that used facial or verbal stimuli, involved central executive engagement as a primary task feature or investigated priming effects, since these tasks fell outside the scope of tasks traditionally examined in visual working memory research, and would unreasonably increase the heterogeneity of the included sample. Tasks were also excluded if performance was at ceiling levels in both control and stress conditions (e.g., as was suggested to explain the lack of significant group difference on the flanker task used by Zhang (2016), which was not included in the present analysis). Several potentially eligible studies explored whether a group difference in spatial strategy (e.g., cue-following vs. way-finding) existed between stress and control groups. In some of these cases, a single task was implemented in a virtual or real environment where external cues marked the walls of the environment. In these cases, the participant was tasked with locating a particular invisible target in the environment. While the target was always in the same position relative to external cues, the vantage point of the participant changed from trial to trial. Importantly, there were two potential

strategies the participant could adopt: a way-finding strategy, where the participant formed a mental representation of the room layout, and mentally rotated this representation upon each change in vantage point, or a cue-following strategy, where the participant learned that the target was next to a specific cue. In order to assess strategy-use, these studies employed a probe trial, where, unbeknownst to the participant, the cue marking the target location was moved to another corner of the environment. If the participant had developed a way-finding strategy, this shift in cue location did not affect task performance. If, however, the participant had adopted a cue-following strategy, performance was impaired. Integral to this paradigm is the integrity of the probe trial. For this reason, care was taken to include such paradigms that used one probe trial only (e.g., Schwabe et al., 2007). This is because paradigms that investigate strategy use on a trial-by-trial basis (e.g., van Gerven, Ferguson, & Skelton, 2016), by introducing a probe trial and changing the cue location after each trial, run the risk of alerting the participant to the change, and biasing strategy use.

If studies used more than one eligible tasks, multiple tasks were included in the analysis (see below for handling of dependence issues), unless there was a valid reason for exclusion. The same was also true for tasks that used more than one outcome measure, although care was taken to avoid overweighting particular outcomes. For example, one study (Guenzel, Wolf, & Schwabe, 2014) included two separate outcome measures that centered on number of errors: number of trials to reach learning criterion (of two error-free trials in a row) and number of errors. In order to avoid overweighting the error outcome measure, only one of these values was included in the current analysis.

### **Coding**

Each study was coded by two independent referees (S.C. and K.V.B). The second referee was blind to specific predictions. An inter-rater reliability analysis was conducted on the following information: a) year of publication; b) final number of subjects analyzed; c) final size of the stress group; d) final number of males; e) final number of females; f) stress type (e.g., cognitive); g) time of day; h) task type (e.g., mental rotation); i) outcomes measured (e.g., percent accuracy); j) retention interval (time between learning and recall); k) relevant results for effect size calculation (e.g., mean control group, mean stress group, standard deviation control group, standard deviation stress group). As described, each task was also coded according to whether it was predicted to experience competition with physical stress (anxious arousal) or cognitive stress (anxious apprehension) (Table 2.1). In cases where literature supported competition with both anxious arousal and apprehension for a particular task, the effects of coding that variable as each possibility were assessed.

### **Calculation of effect sizes**

Effect sizes were defined as the difference between the mean of the control group and the experimental group, standardized by the pooled standard deviation. Effect sizes were calculated using the meta-analytic software program Comprehensive Meta-Analysis (Borenstein, Hedges, & Higgins, 2005). Positive effect sizes ( $g_s$ ) indicate better performance in the stress group, while negative effect sizes indicate better performance in the control group. When a study included more than one task (e.g., both a manipulation and a maintenance task), outcomes for these tasks were averaged for the initial analyses (which examined the global effect of stress on all visual tasks combined), but were then

separated into relevant categories for subgroup analyses (see Analysis of effect sizes, below). Reaction time measures were analyzed separately from accuracy measures.

Studies were weighted by the inverse of the variance of the effect size, and Cochran's Q statistic was used to test the variability across studies (Borenstein, Hedges, Higgins, Higgins, & Rothstein, 2009). A finding was considered an outlier if it was the single extreme value and accounted for approximately 50% of the total variance (Q) (Hanson & Bussière, 1998).

The current meta-analysis included studies with both independent and repeated measure group designs. There are fundamental differences in how variance is conceptualized across these designs, and it is therefore important to account for these differences by normalizing the calculated effect size. In the current analysis, repeated measures effect sizes were transformed into a common metric according to suggestions presented (Morris & DeShon, 2002) in order to avoid biases presented by mixing study designs.

### **Analysis of effect sizes**

As recently noted (Scammacca, Roberts, & Stuebing, 2014), dependence is an important issue in meta-analytic approaches as it influences the heterogeneity of the overall sample. For the current analysis, the decision was made to average effect sizes at the task and outcome level, since assuming a correlation of 1.0 and inflating the chance of type II error led to smaller estimates on the Q index of heterogeneity. Given that one of the hypotheses of the current study was that the variance inherent throughout the stress literature could be in part explained by considering competing ongoing cognitive

processes, I deemed it a safer approach to avoid inflating the heterogeneity by assuming independence.

For each study, the average effect size was calculated using 95% confidence intervals. After using the study as the unit of analysis, it was determined whether the resulting effect sizes could be viewed as coming from a single population. Weighted effect sizes were calculated, and a test of homogeneity ( $Q$ ) was conducted, where a significant result indicated a heterogeneous population. A significance test for publication bias was also conducted.

Subgroup analyses were used to account for significant variability in the overall sample. The categorical subgroups investigated included stress (physical vs. cognitive) and predicted competition (arousal vs. apprehension). Here, two studies contained samples that fell into two categories for the predicted competition subgroup (Gabriel, Hong, Chandra, Lonborg, & Barkley, 2011; Thomas et al., 2014). Despite the suggestion that the treatment of a small relative number of studies as independent will likely not vastly influence meta-analytic results (Scammacca et al., 2014), care was taken to explore various methods of limiting any bias introduced as a result of dependence. Homogeneity of effect sizes within each class ( $Q_T$ ) were examined, and overall homogeneity tested by the within-class-goodness-of-fit statistic ( $Q_W$ ). Homogeneity between subgroups was also tested ( $Q_B$ ).

## **Results**

### **Description of study features**

Of the 4023 hits from the initial literature search, a total of 45 tasks examining 1287 individuals from 35 published studies met inclusion criteria and were deemed

eligible for analysis. Seven studies included a sample of males only, while two studies included a sample of females only. Mean ages ranged from 18.9 to 34 years, with an overall mean of 23.92 years ( $SD \pm 3.34$ ). After conducting the inter-rater reliability, no Kappa statistic or Intraclass Correlation Coefficient (ICC) was below 0.700 for any of the variables investigated. Discrepancies (i.e., statistics below 1.0) were resolved by discussion.

Of the 35 studies examined, 14 used a psychosocial stress task to induce stress (e.g., the Trier Social Stress Task), seven administered a corticosteroid, six used a threat of shock paradigm, three implemented mild physical stress (e.g., the Cold Pressor Test), two used a combined psychosocial and mild physical stressor, one used a time to event stress induction paradigm, one used the star-mirror tracing task and one used a negative stereotype task. Classifications of each paradigm and associated references are presented in (Table 2.2).

### **Effect sizes**

Eleven studies used more than one (eligible) visual task. Most studies also measured task performance using more than one performance measure, in which case one effect size was calculated for each performance measure, and then averaged to give one effect size for each task. While reaction times and accuracy measures were combined in the primary analysis, they were also examined separately (as discussed below).

### **Primary analysis**

I hypothesized that a re-operationalization of stress as anxious arousal or anxious apprehension would better describe the relationship between stress and visual working

memory task performance than previous attempts, which have mainly explored whether stress generally impairs or enhances visual working memory task performance.

As predicted, the overall sample of effect sizes did not pass the test for homogeneity ( $Q = 66.673, p < 0.01$ ), indicating significant variability above that expected by chance. Analyzing effect sizes based on reaction time only (and not accuracy measures) did not change this pattern, nor did analyzing effect sizes based on accuracy measures only. These results justified running subgroup analyses to determine whether variability could be explained in part by a competition for neural resources.

### **Subgroup analyses**

Subgroup analyses were conducted to explain the variability of the overall sample. The moderators examined included the following two groups:

1. *Stressor type*, referring to the stress paradigm utilized (physical versus cognitive), where physical stress is believed to primarily elicit anxious arousal and cognitive stress is believed to primarily elicit anxious apprehension.

2. *Predicted competitor*, referring to the anxiety subtype (arousal vs. apprehension) predicted to compete with and impair the visual task in question.

Because this analysis compared qualitatively different visual tasks and included a variety of stress induction protocols, a random effects model was selected over a fixed-effect model, which assumes only one true effect size. As a first step, separate subgroup analyses were performed using stressor type and predicted competitor as units of analysis. As expected, total within group variance was significantly greater than that expected by chance. The total between group variance using a mixed effect model indicated no significant difference between subgroup in each case. Narrowing outcome

measures by considering performance variables and reaction time outcomes separately did not change this pattern of results.

In order to limit any bias introduced by dependence, the weights of each non-independent sample were artificially reduced and all analyses re-run. The pattern of results discussed previously did not change, with total within group variability being greater than that expected by chance, and with no significant difference observed between subgroups when using both stressor type (physical vs. cognitive) and predicted competitor (arousal vs. apprehension) as units of analysis. These results confirm that the moderators examined do not individually explain the variability of the overall sample, thus justifying the exploration of whether impaired performance would be found in cases when stress induction paradigm and visual task were predicted to engage similar resources.

In order to determine whether resource competition could help explain the heterogeneity observed in previous analyses, two subgroups were created. The first subgroup, labelled “same”, encompassed cases where stressor type and visual task were predicted to occupy overlapping neural resources (i.e., either both engaging intrinsic or both engaging extrinsic network subsystems). These cases included those involving a physical stressor paired with a visual task believed to compete with anxious arousal (i.e., tasks categorized as: maintenance, search, tracking, cue-following and reordering (Table 2.1)), and those involving a cognitive stressor paired with a visual task believed to compete with anxious apprehension (i.e, tasks categorized as: way-finding, manipulation (rotation), spatial reasoning). The second subgroup, labelled “different”, encompassed cases where stressor type and visual task were predicted to rely on non-overlapping

resources. These cases included those involving a physical stressor paired with a visual task believed to compete with anxious apprehension, and those involving a cognitive stressor paired with a visual task believed to compete with anxious arousal. When using these “same” and “different” subgroups as the unit of analysis, a significant difference between groups was observed ( $Q_{between} = 24.603$ ,  $df = 1$ ,  $p < .001$ ), with each passing tests for homogeneity, indicating that these moderators explained the above-chance variability of the original sample. A small to-moderate negative effect size was associated with the “same” subgroup, where neural resources were predicted to overlap. In contrast, a significant small positive effect size was observed for accuracy measures in the “different” subgroup, where less competition for neural resources was predicted (Table 2.4, Figure 2.1). These trends held when considering accuracy measures only. No significant relationship was found for subgroups when examining reaction time only, with both subgroups failing tests of homogeneity.

Further subgroup analyses were conducted in order to explore the pattern of results when collapsed groups were separated out according to the four possible “same”/“different” scenarios. These four groups were named according to the following convention: “Competitor: Stress”. Here, the “Competitor” slot is an attribute of the visual task used in each case, and refers to the anxiety subtype (arousal vs. apprehension) predicted to compete with and impair the visual task in question. “Stress” denotes the stress paradigm utilized (here labelled physical vs. cognitive), where physical stress is predicted to primarily elicit arousal, and cognitive stress is predicted to induce apprehension. As such, the four subgroups were as follows: 1) Arousal: Physical (e.g., maintenance task with threat of shock paradigm), 2) Apprehension: Cognitive (e.g.,

rotation task with Trier Social Stress Task), 3) Arousal: Cognitive (e.g., maintenance task with Trier Social Stress Task), 4) Apprehension: Physical (e.g., rotation task with threat of shock paradigm). When using these “competitor: stress” subgroups as the unit of analysis, and examining combined accuracy and reaction time outcomes, a significant difference between groups was observed ( $Q_{between} = 24.603, df = 1, p < .001$ ), with each group passing tests for homogeneity. Effect sizes under the random-effects model were significant for all subgroups with the exclusion of “arousal:cognitive”. When examining accuracy outcomes only, however, this group was associated with a significant positive small-moderate effect size, with all other trends holding (Table 2.4, Figure 2.2).

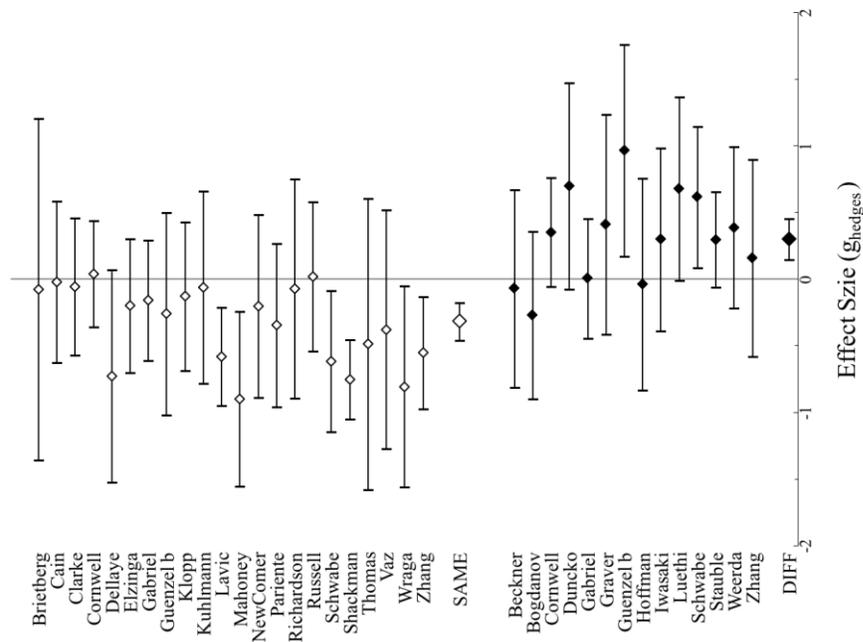


Figure 2.2: Forest plot of effect sizes for Same/Different subgroups and their 95% CIs. Study names are indicated along the x-axis. Effect sizes (*ghedges*) for each Study are denoted by white (Same subgroup) and black (Different subgroup) diamonds, with average effect sizes for each group represented with larger diamonds. Positive values indicate improved performance in the stress relative to control condition.

Table 2.4: Results of moderator analysis

	Competitor: Stress	G	95% CI			N	Q	I <sup>2</sup>
			LB	UB				
All measures								
<b>Same</b>		-0.269**	-0.383	-0.156	22	19.881	10.065	
	<i>Arous.:Phys.</i>	-0.222**	-0.351	-0.092	15	12.524	0.000	
	<i>Appr.:Cog.</i>	-0.424**	-0.658	-0.191	7	5.145	0.000	
<b>Different</b>		0.201**	0.054	0.349	16	15.695	0.000	
	<i>Arous.:Cog.</i>	0.088	-0.090	0.267	11	9.432	0.000	
	<i>Appr.:Phys.</i>	0.404**	0.166	0.642	5	1.949	0.000	
						<i>Between level Q</i>	32.158**	
<b>Between level Q</b>	24.641**							
Accuracy only								
<b>Same</b>		-0.354**	-0.488	-0.219	22	25.937	19.036	
	<i>Arous.:Phys.</i>	-0.325**	-0.501	-0.149	15	21.443	34.709	
	<i>Appr.:Cog.</i>	-0.400**	-0.633	-0.167	7	4.420	0.000	
<b>Different</b>		0.299**	0.143	0.454	14	13.028	0.446	
	<i>Arous.:Cog.</i>	0.227**	0.022	0.431	9	5.768	0.000	
	<i>Appr.:Phys.</i>	0.434**	0.158	0.633	5	6.142	34.878	
						<i>Between level Q</i>	34.091**	
<b>Between level Q</b>	38.838**							
RT only								
<b>Same</b>		-0.060	-0.298	0.177	9	16.676*	52.028	
	<i>Arous.:Phys.</i>	0.010	-0.196	0.217	6	7.857	36.364	
	<i>Appr.:Cog.</i>	-0.627	-1.539	0.284	3	6.806*	73.262	
<b>Different</b>		0.019	-0.319	0.358	6	9.448	47.080	
	<i>Arous.:Cog.</i>	-0.250	-0.562	0.062	3	0.121	0.000	
	<i>Appr.:Phys.</i>	0.349	-0.103	0.801	3	2.876	30.447	
						<i>Between level Q</i>	6.405	
<b>Between level Q</b>	0.143							

Note:  $g = g_{\text{hedges}}$ ; CI = confidence interval; LL = lower bound; UL = upper bound. Arous.:Phys. = arousal: physical; Appr.:Cog. = apprehension: cognitive; Arous.:Cog. = arousal: cognitive; Appr.:Phys. = apprehension: physical. The between level  $Q$  represents the variability across studies due to the moderator variable.

\*  $p < 0.05$ , \*\*  $p < 0.01$ .

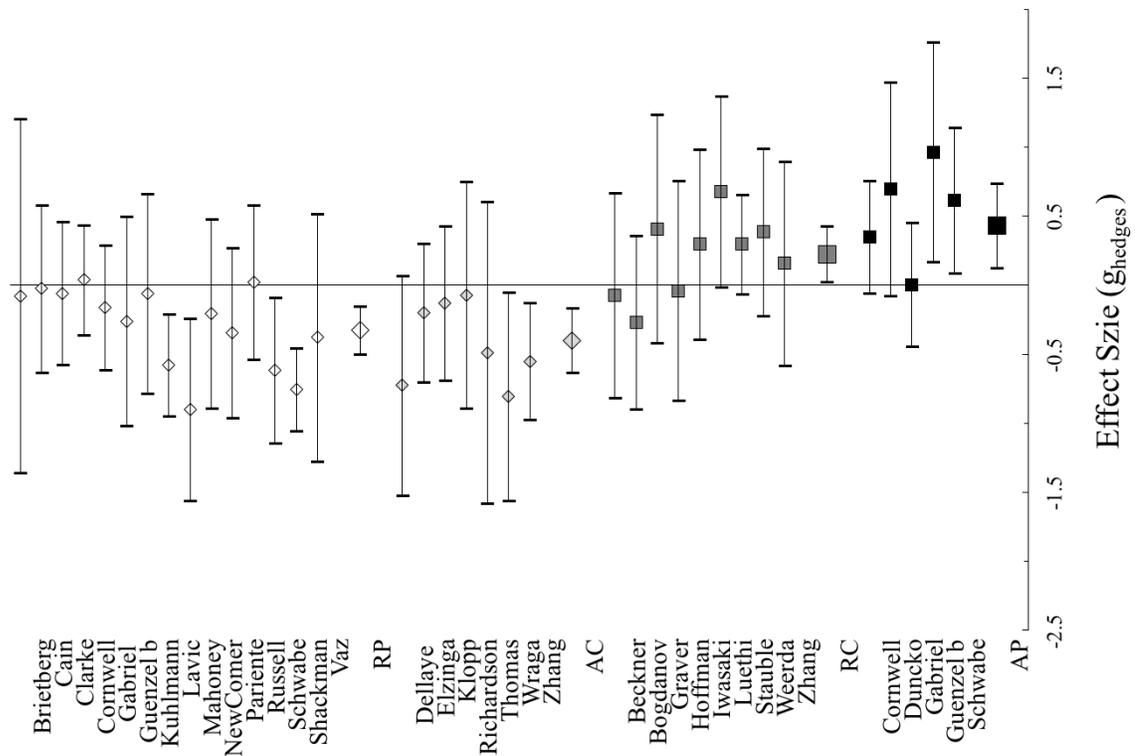


Figure 2.3: Forest plot of effect sizes within Same/Different subgroups and their 95% CIs for each sample and combined weighted average. Study names are indicated along the x-axis. Positive values indicate improved performance in the stress relative to control condition.

## Discussion

The goal of the present quantitative meta-analysis was to explore the dynamics of stress on visual task performance in order to assess whether different functional connectivity patterns likely accompany arousal versus apprehension. Recent evidence suggests that arousal and apprehension induce unique physiological effects and provoke different functional connectivity changes across widespread brain regions that act together as large-scale networks (Liang, Zou, He, & Yang, 2016; Liu et al., 2016; Menon, 2011). While physical stressors induce arousal and reallocate resources away from dorsal

regions governing top-down control of attention to external stimuli, cognitive stressors induce apprehension, and shift activity to areas of the default mode pathway. Given these complex dynamics and the qualitative differences between standard stressor paradigms, there is no reason to expect two particular stressors should influence cognition in the same way. The goal of the current analysis, therefore, was to re-operationalize stress paradigms as primarily eliciting either anxious arousal or anxious apprehension, and to assess whether this re-operationalization could explain some of the variance surrounding stress and visual working memory. Additionally, I examined whether anxiety subtypes differentially constrained two broad classes of visual working memory tasks that differ in their internal/external processing requirements.

A meta-analytic review was conducted on 35 eligible independent studies (pared down from 4023 initial hits) that assessed the effects of stress on various visual storage and processing tasks. These 35 studies were coded according to whether the stressor was physical or cognitive as well as based on whether the visual tasks examined were predicted to compete with arousal or apprehension. Competition was expected in cases where stressors were documented as prompting functional connectivity changes that shunted neural resources from brain regions known to support the visual task in question (Table 2.3). The results of this analysis confirm that operationalizing stress in this way can account for some of the variance surrounding the effects of stress on visual task performance, suggesting that the functional connectivity changes accompanying stress impose different constraints and limitations on visual storage and processing. Broadly speaking, we found that when the stressor and visual task competed for neural resources, performance decrements occurred.

In the current analysis, physical stressors were associated with impaired performance on tasks supported by right-lateralized regions of the dorsal attention network, in particular, the right dorsolateral prefrontal cortex and right posterior parietal cortex (Sridharan et al., 2008). This is in line with the prediction that physical stressors increase anxious arousal and activate a right-lateralized ventral attention network (Corbetta & Shulman, 2002; Ghahremani et al., 2015; Kucyi et al., 2012; Sridharan et al., 2008) involved in bottom-up attention to external stimuli. As stimulus-driven capture of exogenous attention increases with ventral attention network activation, top-down control of attentional filtering for target features decreases and performance suffers on tasks requiring this attentional allocation to visual perceptual stimuli. In contrast to physical stressors, the cognitive stressors examined, which were predicted to increase anxious apprehension and unconstrained internally-directed thought, led to a performance decrement on tasks requiring top-down attentional allocation to stimulus-independent internal representations. Among other task types, this included a performance decrement on mental rotation tasks, which have been noted to involve left-lateralized regions of the central executive subsystem as well as sub-regions of the default mode network (Gao et al., 2017).

It was predicted that physical and cognitive stressors would compete with task performance in “same” subgroups, that is, tasks that rely on right-lateralized areas of the dorsal attention network and left-lateralized regions of the central executive network (respectively). However, no a priori prediction was made regarding expected outcomes in “different” subgroups. Interestingly, “different” subgroups were generally characterized by significant positive effect sizes, such that physical stressors led to

improved performance on tasks believed to rely on controlled attention to internal representations, while cognitive stressors led to improved performance on tasks relying on top-down allocation of attentional resources to external perceptual stimuli. While caution should be taken when interpreting these results, recent evidence describes antagonistic relationships between relevant network nodes that might help to explain the pattern observed here. One of these relationships involves dissociated functional connectivity between two subregions of the temporoparietal junction (TPJ): the anterior TPJ, which shows connectivity with the ventral attention/salience network, and the posterior TPJ, which is coupled to the default mode network (Bzdok et al., 2013; Mars et al., 2012; Trautwein, Singer, & Kanske, 2016)). While increased anterior insular activity observed during reorienting and executive control is correlated with increased activity in right anterior TPJ (consistent with its coupling to the ventral attention network), it is associated with decreased activity in left posterior TPJ and precuneus—a region of the core default mode network (Trautwein et al., 2016). The latter reduction in activity is thought to reflect the downregulation of processes unrelated to task completion or unwanted thought during periods of increased attentional demand (Trautwein et al., 2016). In essence, as ventral attention network activation down-regulates regions of the default mode network that otherwise compete with attention to internal representations, performance improves on visual tasks requiring the creation of a mental image for subsequent processing. This relationship is consistent with other research that suggests arousal improves performance on tasks that rely on left posterior parietal areas, including visualization tasks like mental rotation (Borst, 2010, 2012, 2013; Mammarella, 2011).

Anxious apprehension, elicited by cognitive stressors, was associated with enhanced performance on tasks requiring top-down control of the dorsal attention network. While perhaps seeming counter-intuitive that increased self-directed thought might improve performance on tasks requiring allocation of attention to external stimuli, another antagonistic relationship offers some insight as to why this might be the case. Research has pointed to the posterior cingulate cortex (a region of the core default node network) as a potential mechanism for regulating activity in the ventral attention/salience network (Seeley et al., 2007; Uddin, Clare Kelly, Biswal, Xavier Castellanos, & Milham, 2009). This regulation occurs as increased internally-directed focus and rumination reduce ventral attention network connectivity (of the right temporoparietal junction (Bijsterbosch et al., 2014) and right inferior frontal gyrus (Kühn, Vanderhasselt, Raedt, & Gallinat, 2013), respectively). Indeed, when temporoparietal junction activity is suppressed during encoding of visual stimuli, visual working memory performance on select tasks has been observed to improve (Anticevic, Repovs, Shulman, & Barch, 2010). This relationship suggests that increased default mode network activity accompanying anxious apprehension may reduce stimulus driven attention to external stimuli and improve performance on tasks requiring right-lateralized top down control. This relationship is parsimonious with the theory that decoupling attention from external perceptual environment insulates internally-directed thought against distraction (Christoff et al., 2016). The reduction of stimulus driven re-orienting might have the unintended benefit also decreasing external distraction, explaining the pattern of results observed in the present analysis.

### Summary

The current meta-analysis is the first to explore how functional connectivity changes accompanying anxious apprehension and anxious arousal influence visual storage and processing tasks. The conceptualization of the brain as consisting of large-scale interactive networks has gained support over the last decade, and although complex, is proving fruitful in uncovering many nuanced relationships. While many variables remain to be elucidated, this meta-analysis suggests that arousal-induced circuit breaking of the dorsal attention network by increased ventral attention network activity impairs performance on visual tasks requiring top down attentional control to external stimuli. The present study also suggests that unconstrained internally-directed thought prompted by increased connectivity within the default mode network during apprehension interferes with tasks relying on left-lateralized central executive and default mode regions. These results provide initial support for a double dissociation effect of stress on visual task performance, such that arousal impairs storage but not manipulation, while apprehension impairs manipulation but not storage, pointing to differential network dynamics between these two task categories. In addition to having practical application, the current results also have implications from a theoretical perspective of visual working memory. At the very least, this meta-analysis suggests that a consideration of which intrinsic/extrinsic network elements are required for successful task performance, as well as how these large-scale networks change with changing contexts can help to predict performance constraints. In order to investigate this idea further, the next chapter presents a controlled study that examines the influence of psychosocial stress on visual maintenance and manipulation.

## References

\*References marked with an asterisk indicate studies included in the meta-analysis\*

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### **Chapter 3: The Influence of Psychosocial Stress on Visual Working Memory**

#### **Introduction**

The meta-analysis presented in Chapter 2 demonstrated that functional connectivity changes within and between large-scale brain networks can impose different constraints and limitations on task performance. The primary aim of the previous meta-analysis was to confirm the idea that different functional connectivity patterns accompany anxious arousal and anxious apprehension. In particular, these results suggest arousal-induced circuit breaking of the dorsal attention network by increased ventral attention network activity may impair performance on visual tasks that require top down attentional control to external stimuli. In contrast, unconstrained internally-directed thought during apprehension may interfere with tasks that rely on left-lateralized central executive and default mode regions.

A secondary aim of the meta-analysis presented in Chapter 2 was to investigate how the distinct cognitive states associated with each anxiety subtype constrain different visual working memory tasks depending on task requirements. To this end, I created two broad task categories with differential exogenous/endogenous processing requirements in order to assess how arousal and apprehension impact visual working memory. While this classification seemed to account for some of the variance in the sample of studies analyzed, qualitative differences between tasks were found even within categories. This finding was not entirely unexpected given the heterogeneity across experimental tasks often employed throughout the visual working memory literature. This typical variance

introduced by the random distribution of effect sizes is further compounded by methodological variability between studies due to differences in experimental design and the populations under investigation. In order to further investigate the idea that visual tasks vary in exogenous versus endogenous attentional requirements such that ideal network dynamics differ between tasks, it is important to conduct a controlled study. To this end, the current chapter presents an experiment designed to investigate the differential effect of anxious apprehension on two visual working memory tasks: a delayed-match to sample task requiring the temporary maintenance of a visual stimulus across a short delay period, and a rotation task involving the mental rotation of the same stimulus pattern.

Previous research documents activation in regions of the default-mode network and left-lateralized regions of the central executive network during mental rotation and visual imagery tasks (Alivisatos & Petrides, 1997; Gao et al., 2017; Lamp, Alexander, Laycock, Crewther, & Crewther, 2016; Wolbers, Schoell, & Büchel, 2006; Zimmer, 2008). Despite this, it is unclear exactly what it is about these tasks that prompts this activation. In the past, default mode regions have been associated with task-negative activity because of their increased activation levels during rest (Andrews-Hanna, 2012; Fox et al., 2005). However, more recently, the activation of key default mode regions, especially in the left hemisphere, has emerged as a stable feature of task-positive mental rotation activity. While some research emphasizes a role of these regions in the image generation component of classical “internally-directed” tasks like mental rotation (Gao et al., 2017), others suggest this recruitment supports the manipulation component of task performance (Schlegel et al., 2013). The nature of central executive involvement is also

contentious, largely because it is difficult to disentangle its role in general attentional requirements from imagery/manipulation demands.

While it is challenging to delineate the supporting role played by default mode and central executive regions throughout imagery-based internal mental manipulation, and to distinguish these roles from the temporary maintenance of information often required in visual working memory tasks, several considerations can help to make this more feasible. First, it is important to design tasks that are as “unalloyed” as possible. That is, tasks should not unreasonably intertwine the elements being investigated. Second, tasks should be similar enough to rule out differential processing requirements invoked by the stimuli themselves. Tasks should not involve drastically different visual stimuli (such as pictures of landscapes in one case, and combinations of geometric shapes in another). Finally, it is important to include more than one workload version of each task under investigation. This allows for the examination of how changing attentional requirements affect performance and accommodates for the possibility that individuals may use different strategies depending on task difficulty; such strategy shifts may alter the dynamics involved.

Keeping these criteria in mind, the aim of the present study was to investigate the influence of anxious apprehension induced by a psychosocial laboratory stressor on two visual working memory tasks. Stimulus features of the two tasks were controlled in order to eliminate the confounds discussed above, while calling for differential maintenance and manipulation requirements of an internal representation. Two workload versions were created for each of two tasks: a mental rotation task requiring the imagery-based internal mental manipulation of a grid pattern (with no maintenance requirement), and a

delayed match-to sample task requiring the temporary maintenance of a similar grid pattern across a short delay period. The previous research discussed, as well as findings from the meta-analysis presented in Chapter 2, suggest that the delayed match-to sample task relies more on right-lateralized regions of the dorsal attention networks, whereas the mental rotation task necessitates a higher degree of internal visualization and processing requirements afforded by left-hemispheric brain regions (of both the default mode and central executive networks). Because of these network differences, it was predicted that the anxious apprehension evoked by our psychosocial laboratory stressor would tax the left-hemispheric resources required for mental rotation, and thereby impair performance on this task.

### **Methods**

This study was conducted as part of a larger study that considered stress effects on cognitive function.<sup>1</sup> In this work, cortisol was measured in order to index participants' physiological stress response to a psychosocial stressor.

#### **Participants**

Carleton University undergraduate students (20 males, 24 females) ranging in age from 18-26 years (Mean age = 20.17,  $SD = 2.25$ ) participated in the study. No participant reported a physical illness/condition at the time of the study, although five reported an anxiety or depressive disorder diagnosis. None of the participants were taking anti-inflammatory, anxiety, nor depressant medications. Of the female participants, 10 were taking an oral contraceptive.

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<sup>1</sup> I gratefully acknowledge the contribution of Robert Gabrys, who at the time of this work was a PhD candidate in Carleton University's Department of Neuroscience.

### **General Procedure**

University students were recruited through Carleton's SONA system. Participants were directed to the Qualtrics webpage for a brief pre-screening questionnaire administered to identify any exclusion criteria. Participants were excluded from this study if they reported any discomfort with the blood collection procedure, previous adverse reactions to donating blood, or the presence of any medical conditions or medications that would interfere with cortisol production and release, as well as production and release of any biomarkers relevant to the parallel study (e.g., of cytokines). Participants who met eligibility criteria were randomly assigned to either the stress ( $n = 21$ ) or control ( $n = 23$ ) condition and invited to participate in the laboratory session.

### **Laboratory Session**

All procedures in this study were approved by the Carleton University Ethics Committee for Psychological Research. Laboratory sessions were conducted between 13:00 and 17:30 hours. All participants were asked to not eat, drink (with the exception of water), smoke, or exercise for at least an hour before arriving to the session.

Upon arrival to the lab, participants who met the screening criteria were asked to read and sign a general informed consent. Following informed consent, participants completed a brief package of questionnaires (15 minutes) which included demographic information, questions regarding brain injury history and depressive symptoms (most of which were relevant to the parallel study). At 15 the minute mark, a registered nurse inserted a catheter into the participant's non-dominant arm for blood collection.

Participants were then asked to relax for an additional 10 minutes. Following the first set

of questionnaires, participants in the stress group were administered a stress induction task while participants in the control group were administered a mental writing task designed not to elicit stress (15 minutes). A second set of questionnaires (15 minutes) assessing stress appraisal was then administered. Experimental tasks, including a cognitive flexibility task and two working memory tasks were then completed by the participants, followed by a third set of questionnaires assessing cognitive flexibility, difficulties in emotion regulation, and emotional strategies. Upon completion of the questionnaire package, participants were informed of the nature of the experiment.

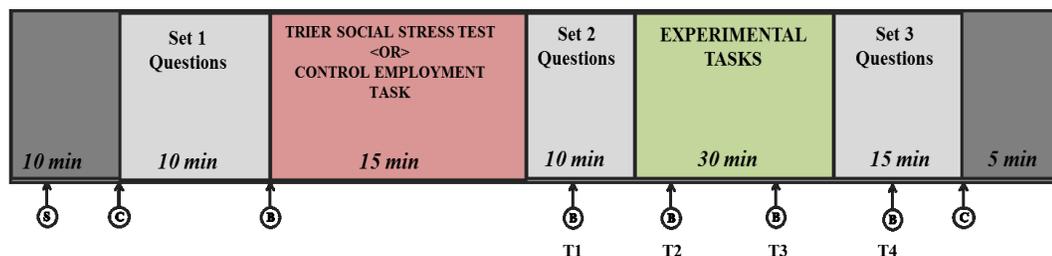


Figure 3.1: Experimental timeline. Arrows indicate collection of blood samples (B) and saliva samples (S) as well as catheter insertion (first C) and catheter removed (second C). T = time.

**Trier Social Stress Test.** As mentioned, following the completion of the first set of questionnaires, participants were assigned to either the stress or control condition. The stress condition comprised the Trier Social Stress Test (TSST) which is a widely used laboratory task designed to elicit a psychological and physiological stress response. The test mainly consists of a public speaking task (5 minutes) and a subsequent mental arithmetic task (5 minutes) in front of an audience of graduate students. Participants in the control condition were asked to complete a mental writing task, which consisted of writing about their strengths and past work/volunteer experiences.

**Blood Collection.** Prior to and at several points following the TSST, blood samples were obtained through an indwelling catheter. Blood samples were collected continuously, using a Dakmed ambulatory pump, at a low draw rate (2.08mL/5min) into chilled EDTA coated vacutainer tubes. For each time-point of interest, samples were taken at an increased draw rate (6.9mL/5min). These time-points included: i) immediately before the TSST or control task (25 minutes after the participant's arrival to the study session), and then at ii) 5, iii) 15, iv) 30, and v) 45 minutes post-task. Approximately 2.76mL of plasma was collected for each of the time-points of interest. Following collection, plasma samples were centrifuged for 15 minutes at 4°C and 2100g, and were immediately aliquoted into Eppendorf tubes and frozen at -80°C. Of the 44 participants, there were 3 individuals from whom blood samples could not be obtained due to complications with small veins.

### **Measures**

**Stress and mood appraisals.** Following stress induction or the control task, participants completed a questionnaire related to stressor appraisals and mood. Stress appraisal measures were taken included: the 28-item Stress Appraisal Measure (SAM; Peacock and Wong, 1990), which focused on threat, control-self, and uncontrollability; the 41-item Positive and Negative Affect Schedule (PANAS; Watson et al., 1988); and a 26-item Cognitive Flexibility Questionnaire (Gabrys, Matheson, & Anisman, in submission).

### **Experimental Tasks**

Following the completion of the TSST and control conditions, participants were asked to complete a series of computerized tasks. The visual working memory tasks,

initiated 15 minutes post-TSST, consisted of two versions each (low workload and high workload) of a visual storage task and a visual manipulation task created based on the results of a pilot study. Pilot research confirmed that the high workload conditions were significantly more difficult than the low workload conditions, and that high workload performance was comparable across task type.

***Visual Storage Task.*** The Visual Storage task was a computerized delayed match-to sample task. In each trial, the participant was presented with a task screen containing a matrix grid (5x5 grid, low workload; 7x7 grid, high workload). A subset of the matrix cells in each grid were shaded, creating a matrix pattern (4, low workload; 7, high workload). A delay screen of 3000 ms was then presented, followed by a second matrix grid which either did or did not match the original grid. Using a response pad, the participant responded “yes” for a match and “no” for a non-match.

***Visual Manipulation Task.*** The Visual Manipulation task was a computerized modified mental rotation task that used the same grid patterns used in the Visual Storage task. In each trial, the participant was presented with a task screen containing two matrix grids side-by-side (5x5 grids with 4 shaded cells for the low workload condition, 7x7 grids with 5 shaded cells for the high workload condition). The participant determined whether the matrix closest to the right side of the screen was a rotated version of the matrix closest to the left side of the screen (rotated 90 degrees to the right). As in the visual storage task, the participant responded via response pad. This task reduced the storage load that traditional mental rotation tasks inadvertently place on participants by using 2-dimensional shapes that are not overly complex, and by displaying both matrices

on the screen simultaneously. Thus, the original stimulus was still available for reference.

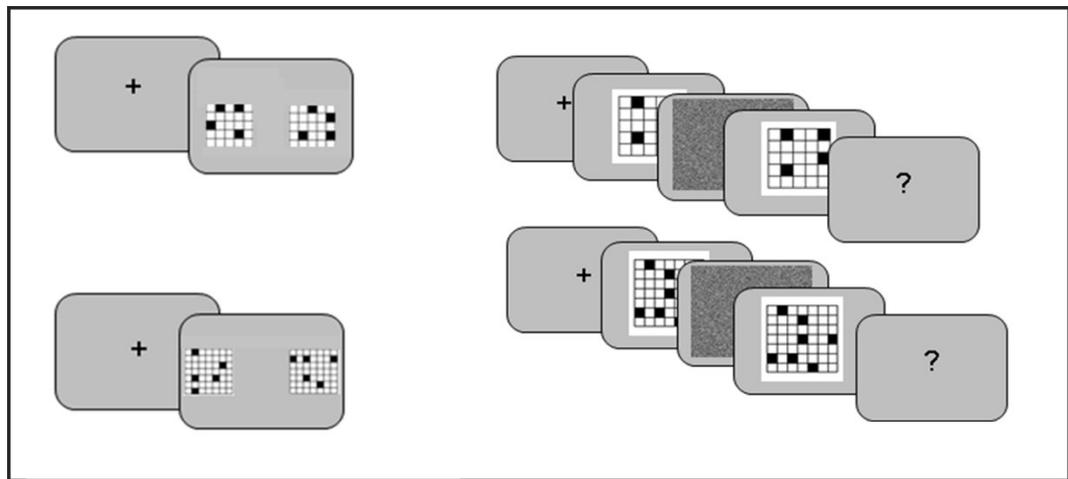


Figure 3.2: Experimental tasks. The visual processing tasks (left) and visual storage tasks (right) each consisted of a low workload (top) and high workload (bottom) version.

### Analyses

Statistical analyses were performed using SPSS for Windows 18.0 (SPSS Science, Chicago, Illinois, USA). Analyses assessing the influence of the TSST on stress appraisals and task performance were performed using a one-way analyses of variance (ANOVA) (Group: stress versus control). Cortisol was analyzed using a 2 (Group) x 5 (Time: 5 time-points) mixed measures ANOVA with Time serving as the within-group factor. Cortisol was assessed using an area under the curve (AUC) analysis (Pruessner, Kirschbaum, Meinlschmid, & Hellhammer, 2003) with group serving as the between groups factors. Follow-up comparisons were comprised of t-tests with a Bonferroni correction to maintain the alpha level at 0.05. Mediation analyses were conducted where relevant to examine direct and indirect relationships.

## Results

### Stress appraisals and mood immediately post-stressor

Immediately following stress induction (Time 1), individuals in the stress group appraised the situation as more threatening than individuals in the control group  $F(1, 42) = 26.62, p < .001, \eta^2 = .39$ , uncontrollable  $F(1, 42) = 8.40, p = .006, \eta^2 = .17$ , less controllable-by-self  $F(1, 42) = 37.08, p = .001, \eta^2 = .24$  and reported higher levels of negative affect,  $F(1, 42) = 8.65, p = .005, \eta^2 = .17$ .

### Cortisol response

A repeated measures ANOVA revealed a significant interaction between Time and Group  $F(4, 36) = 4.67, p = .004, \eta^2 = .34$ . While control and stress groups did not significantly differ at baseline  $F(1, 39) = 4.77, p = .035$ , nor 5 minutes post-TSST  $F(1, 39) = 2.04, p = .161$ , cortisol levels were significantly higher in the stress group 15 minutes  $F(1, 39) = 4.55, p = .039$  and 30 minutes  $F(1, 39) = 7.63, p = .035$  post-TSST (Figure 3.3). A single measure of cortisol response was computed (AUCi), which was found to be significantly higher in the stress group ( $M = 201.71, SD = 168.74$ ) than the control group ( $M = -15.58, SD = 211.79$ ),  $F(1, 39) = 13.12, p = .001, \eta^2 = .25$ .

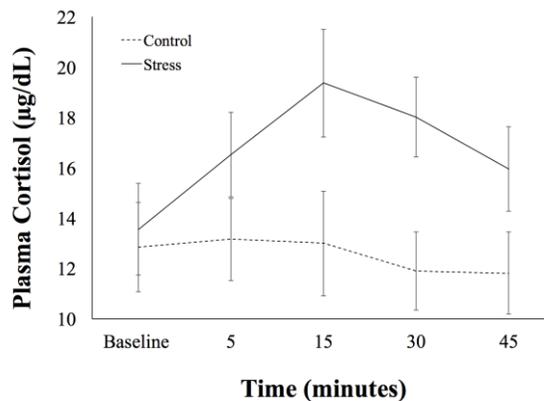


Figure 3.3. Cortisol response for control and stress groups at baseline and each of the four time points. Error bars represent standard deviations.

### Working memory

The comparison of stress and control groups in a 2 (Group: control vs. stress) x 2 (Workload: low vs. high) mixed design revealed a main effect of workload such that percent accuracy was higher in the low-workload group for both the match ( $F(1, 42) = 129.833, p < .001, \eta^2 = .0756$ ) and rotation tasks ( $F(1, 42) = 29.748, p < .001, \eta^2 = .415$ ). There were no significant differences in performance on either working memory task between the stress and control group  $F(4, 36) = .78, p = .543, \eta^2 = .08$ . Specifically, as shown in Figure 3.4, individuals in the stress and control groups did not perform differently on the low workload ( $F(1, 39) = 2.27, p = .140, \eta^2 = .06$ ) nor high workload ( $F(1, 39) = .01, p = .919, \eta^2 = .00$ ) delayed match-to sample task. Additionally, individuals in the stress and control groups did not perform differently on the low workload ( $F(1, 39) = .54, p = .469, \eta^2 = .01$ ) nor high workload ( $F(1, 39) = .65, p = .425, \eta^2 = .02$ ) versions of the mental rotation task.

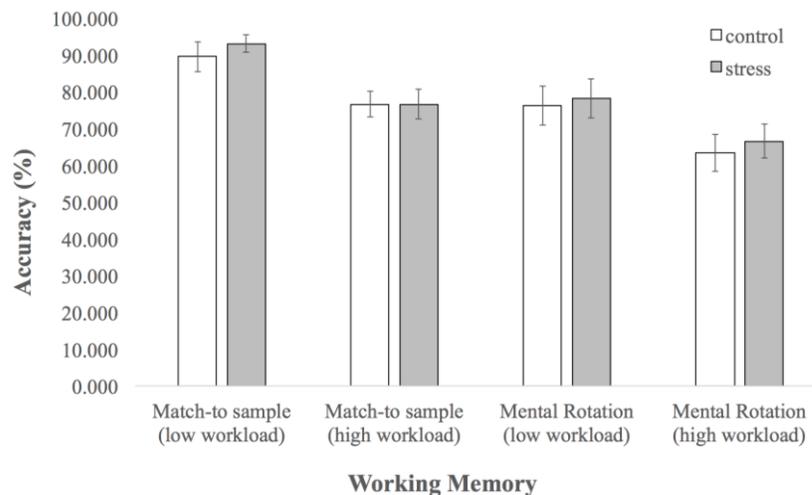


Figure 3.4. Percent accuracy of delayed match-to sample and mental rotation tasks at low and high workloads for control and stress groups. Error bars represent 95% confidence intervals.

Reaction time was lower in the low-workload group for both the match  $F(1, 36) = 617.638, p < .001, \eta^2 = .972$  and rotation tasks  $F(1, 36) = 14.545, p < .001, \eta^2 = .288$ . There were no significant differences in reaction time on either working memory task between the stress and control group  $F(4, 36) = 1.067, p = .377, \eta^2 = .088$ .

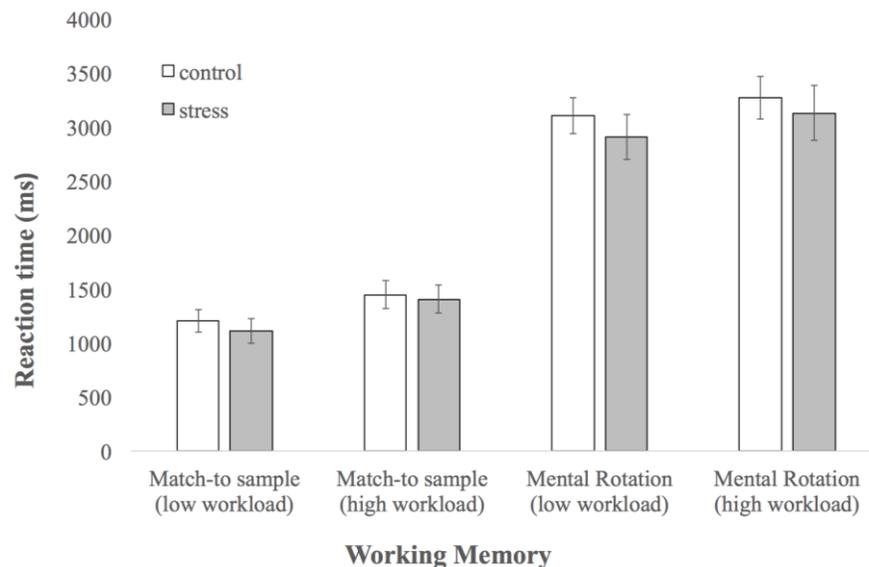


Figure 3.5. Reaction time of delayed match-to sample and mental rotation tasks at low and high workloads for control and stress groups. Error bars represent 95% confidence intervals.

### Relationship between stress appraisals, cortisol response, and working memory

Despite the absence of a main effect of stress on working memory performance, zero-order correlations revealed that perceptions of uncontrollability were associated with lower accuracy on the mental rotation task (see Appendix A for summary of zero-order correlations for both match-to sample and mental rotation tasks). To investigate this further, mediation analyses were conducted. While researchers have traditionally maintained that evidence of an association between X and Y must be established prior to mediation analyses, this restriction is no longer imposed in scholarly circles of mediation analyses (Hayes, 2013). While there was no evidence of a *direct* association between

stress and mental rotation performance in the current experiment, mediation analyses were deemed acceptable based on theoretical grounds. In particular, the meta-analysis presented in the preceding chapter was conducted in order to aggregate information across studies in attempt to increase statistical power, such that the small effect sizes characteristic of stress and cognition research could be drawn out. Results of this analysis point to an association between apprehension and mental rotation performance, and guided a priori predictions and the theoretical framework employed here.

Mediation analyses revealed that the stress group was associated with increased perceptions of uncontrollability relative to the control group ( $b = .85$ ,  $S.E. = .27$ ) and that this in turn was related to decreased performance on the mental rotation task ( $b = -0.5$ ,  $S.E. = 0.02$ ; pooled workloads). A significant indirect effect was observed (95% C.I.:  $-.09, -.01$ ).

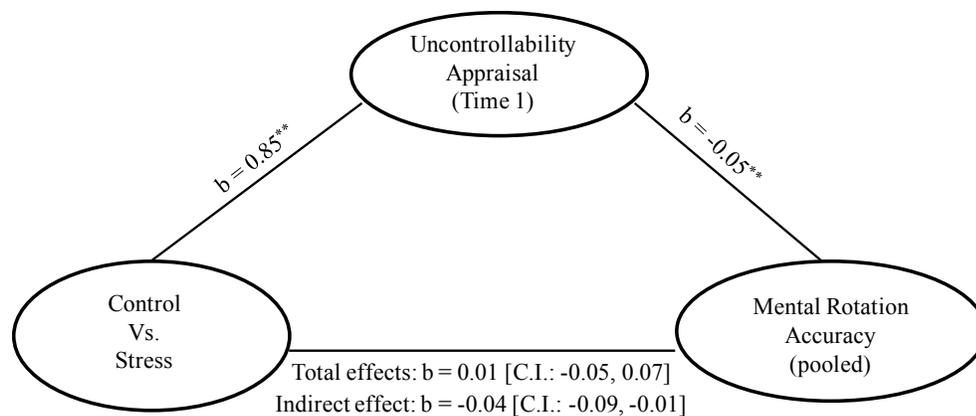


Figure 3.6. Simple mediation model for influence of uncontrollability on mental rotation

## Discussion

The present study examined the influence of a social-evaluative lab stressor on two visual working memory tasks with differential storage and manipulation requirements. Based on a prior meta-analytic experiment (Chapter 2), it was assumed

that the delayed match-to sample task would rely more on regions of a right-lateralized dorsal attention network, whereas the mental rotation task would require internal visualization and processing requirements supported by left-hemispheric brain regions. It was predicted that the psychosocial lab stressor would predominately elicit anxious apprehension, thereby taxing left-hemispheric resources, resulting in impaired performance on the mental rotation task. While an overall impairing effect of stress on mental rotation was not found, analysis showed a significant mediating effect of controllability. More specifically, decreased perceptions of control resulted in impaired performance. While no direct effects were discovered, research related to perceptions of control may help to make sense of the mediation effect observed. This rationale is based on a summary of the neurochemical and neuroanatomical underpinnings of control perception (Declerck, Boone, & De Brabander, 2006), which will be briefly summarized here.

According to Declerck, Boone and De Brabander (2006), an individual's "locus of control" relates to how a person attributes control over environmental outcomes to one's-self. "Internals" attribute this locus of control to themselves, and believe particular outcomes are contingent on their behaviour, while "externals" tend to believe outcomes are more random, and that they have little control over events. It is important to note that this locus of control - whether an individual is an internal or external - is a durable personality trait that persists over time. However, this trait has been described as fluctuating depending on momentary perceptions of control. So, while we cannot necessarily assume those individuals who reported high levels of uncontrollability in the current study have an external locus of control as a durable personality trait, it is

reasonable to speculate that in response to the lab stressor introduced, these individuals had a higher perceived sense of external control than those who felt more in control of the situation (Declerck et al., 2006). Despite these caveats, and for the sake of simplicity, I will use the terms “external” and “internal” to describe those individuals in the current experiment who reported lower versus higher levels of controllability, respectively.

An “activation-arousal” model (Liotti & Tucker, 1996) explains how certain personality traits, including the locus of control, may stem from differences in dopamine neural pathways – pathways that dictate an individual’s responsiveness to external stimuli. These pathways are “noradrenergic arousal” and “dopaminergic activation”. Noradrenergic arousal involves the locus coeruleus and has widespread innervations to the limbic system through the cortex (especially in the right lobe). This attention system achieves its regulatory role primarily through applying a habituation bias, resulting in a greater likelihood that the brain responds to novel items (Tucker, Vannatta, & Rothlind, 1990). Dopaminergic activation, in contrast, is regulated by dopaminergic neurons originating in the ventral tegmental area of the midbrain with connections to the motor cortex, anterior cingulate gyrus and frontal cortex (especially in the left lobe). This system achieves regulatory control by restricting the rate of change of information processing. Because of the distribution of these pathways, noradrenergic arousal and dopaminergic activation are lateralized, and different individuals tend to depend more on one versus the other for self-regulatory control. While an individual who relies more on noradrenergic arousal for self-regulatory control may have an advantage with holistic or global processing, an individual who is governed by dopaminergic activation may have more success with skills that depend on routinization, such as maintaining order

(Declerck et al., 2006).

Declerck et al. (2006) suggest individual variation between these two pathways leads to personality differences in locus of control, such that externals are dominated by right-lateralized noradrenergic arousal, while internals are dominated by left-lateralized dopaminergic activation. These asymmetric neurochemical pathways that underlie self-regulation styles (Heilman, 1995; Posner, 1995; Robbins & Everitt, 1995; Tucker & Williamson, 1984; Witting, 1995) are also expected to lead to predictable differences in the cognitive functions they sustain. While internals have superior ability on left-lateralized tasks, especially on verbal tasks and those relying on frontal executive functions sustained by the left hemisphere, externals have superior abilities related to spatial and configurational cognitive skills of the right-lateralized dorsal corticolimbic pathways (Liotti & Tucker, 1995; Perner & Lang, 1999). Experimentally, individuals with an internal locus of control show more focused attention when primarily left hemispheric/ventral tegmental pathways are engaged in a task. In contrast, individuals with an external locus of control are more susceptible to distraction by an unexpected priming stimulus during visual tasks relying on right-hemispheric pathways. Interestingly, no impairment (relative to baseline) occurs when this unexpected stimulus is presented to externals completing a left-hemispheric task (De Brabander, Boone & Gerits, 1992; De Brabander et al., 1990a; De Brabander, Gerits & Boone, 1990b). If this activation-arousal model holds, it follows that in our study, externals were more likely to rely on a right-lateralized, noradrenergic arousal system as a form of self-regulation while internals were governed by a left-lateralized dopaminergic complement. A greater relative ability of internals to show continued focused attention in the face of distraction,

especially on left-hemispheric tasks, may explain why these individuals out-performed externals on our mental rotation task after stress induction.

Interestingly, the lateralized brain activity supporting internal versus external self-regulatory styles parallels the dichotomy in intrinsic versus extrinsic networks discussed in Chapter 2. As discussed previously (Chapter 1), a main hierarchical division splits these large-scale networks into “extrinsic” and “intrinsic” systems. The extrinsic network interfaces with the external world, while the intrinsic network directs attention and processing toward internal representations (Doucet et al., 2011; Hacker, Snyder, Pahwa, Corbetta, & Leuthardt, 2017; Zabelina & Andrews-Hanna, 2016). The noradrenergic pathway that dominates self-regulation amongst externals overlaps with right-lateralized regions of the ventral attention network – a subsystem of the extrinsic pathway discussed in Chapter 2. This pathway also supports orienting to novel information in the environment (Tucker et al., 1990), which explains why externals are more susceptible than internals to distraction from an unexpected stimulus. The dopaminergic pathway, in contrast, is more left-lateralized, and allows internals to maintain sustained endogenous attention especially on tasks that recruit left-hemispheric regions of the central executive and default mode pathways, like mental rotation.

The mental rotation task required several steps for successful completion: individuals had to encode a visual stimulus, generate an internal representation of this stimulus, mentally manipulate this internal representation by rotating it 90 degrees, and finally, had to compare it to a second stimulus (responding accordingly). While previous research highlights the role of left hemispheric brain regions in mental rotation tasks (Alivisatos & Petrides, 1997; Gao et al., 2017; Lamp et al., 2016; Wolbers et al., 2006;

Zimmer, 2008), it has been difficult to decipher exactly what element of the task prompts this activation. In the current experiment, visual stimuli were controlled across the mental rotation and delayed match-to sample tasks to avoid confounds introduced by differences in feature processing at encoding. The storage requirement in the mental rotation task was also reduced by giving the participant access to the original stimulus throughout the entire task. These design features minimized noise from task-irrelevant demands while altering maintenance and processing requirements between tasks, and therefore increase confidence that the mediation effect observed here owed to the imagery-based internal mental manipulation requirement of our mental rotation task. The fact that there was no direct effect (nor any mediation effect) of stress on the delayed match-to sample task suggests that maintenance processes supporting storage are different from those supporting mental rotation. Domain-general executive processing requirements can also be ruled out as contributing to the observed effects, since increased processing demands associated with higher workload versions of the task did not induce systematic effects. If, for example, the increased performance of internals on mental rotation reflects their superior ability to maintain attention more generally, then we would have expected systematic out-performance of externals by these individuals on both task types. Additionally, although not a focus of the current study, there was no effect of stress on the Wisconsin Card Sort performance, a classic task used to probe executive function (and bilateral frontal lobe functioning) (e.g., Arnett et al., 1994).

The strict eligibility requirements of this study, paired with the fact that it necessitated blood collection, made it difficult to foster consistent participation (as represented by our relatively low sample size despite having run the study for over two

years). Because of this low power, many of the genotypic investigations that could have shed further light on, and perhaps corroborated the speculative group differences discussed here were foregone. Nevertheless, the mediation effect observed is suggestive. One remaining question in particular warrants further investigation, which relates to the nature of “imagery-based internal mental manipulation”. While interpretations presented here are consistent with previous work that documents left-hemispheric activation during imagery-based internal mental manipulation, and suggests that there are key differences between the simple maintenance of visual information and the manipulation of an internally generated representation, it is still unclear whether these key differences occur because the nature of the internal representation formed during rotation is different from that maintained during the delayed match-to sample task. Past research suggests a role of left lateralized regions in visualization and imagery. However, the question remains whether this type of activation should be expected for the maintenance of a visual representation. In order to investigate this question, the next chapter presents an electroencephalographic experiment that aims to identify source localizations during the maintenance period of our delayed match-to sample task, and explores potential changes in brain dynamics instigated by an exogenous distractor.

### **Summary**

The current study examined the influence of a stressor designed to elicit anxious apprehension on visual maintenance and mental rotation. Based on previous research, I predicted that processes associated with lab-induced anxious apprehension would activate left-lateralized regions of the intrinsic network (of the central executive and default mode

networks in particular). I also predicted that this pattern of network activity would constrain mental rotation, which implicates intrinsic network regions that overlap with those activated during anxious apprehension. While no main effect of apprehension on task performance was observed for either task, a mediation effect was found whereby individuals with an internal locus of control (internals) out-performed those with an external locus of control (externals). An activation-arousal model suggests a greater relative ability of internals to show continued focused attention in the face of distraction, especially on left-hemispheric tasks. This model supports the interpretation that internals outperformed externals only on the mental rotation task (and not the visual maintenance task) after stress induction due to a greater ability of sustained top-down control to internal representations in the face of endogenous distraction. The fact that no mediation effect was observed for visual maintenance points to a dissociation in the large-scale network dynamics that support maintenance and manipulation within visual working memory more generally.

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## **Chapter 4: EEG Correlates of a Delayed Match-to Sample Task**

### **Introduction**

The meta-analysis and stress study presented earlier (Chapters 2, 3) suggest key differences between the maintenance and manipulation of visual information that may occur in part because of the variable interplay between extrinsic and intrinsic networks, as discussed. The overarching aim of the current thesis has been to understand the neural mechanisms of visual working memory, and to uncover patterns of interaction that support these cognitive processes. To this end, I have used two exemplar tasks that are often employed in cognitive research – a delayed match-to sample task that emphasizes storage requirements and a mental rotation task that involves manipulation. While both of these tasks require the encoding of perceptual input and an interaction with a represented version of this input, they are qualitatively different. My aim has been to determine whether these differences translate to distinct neural activity and whether this activity leads to predictable behavioural performance with changing cognitive constraints. In order to achieve this aim, I used complementary methodologies as urged by recent research that emphasizes the importance of characterizing connectivity changes with synergetic protocols (Daniel, Katz, & Robinson, 2016; Owen, McMillan, Laird, & Bullmore, 2005). First, I performed a meta-analytic survey in order to theoretically investigate the dynamic interplay between intrinsic and extrinsic network activity. Second, I performed a controlled stress experiment in order to more systematically

explore how the bottom-up capture of internal attention by anxious apprehension differentially influences performance on a delayed match-to sample task versus a mental rotation task. Importantly, the tasks used were controlled in order to avoid several limitations inherent in other research designs. In particular: matrix grids were used as visual stimuli in order to reduce the likelihood of verbal coding; identical matrix grids were used between tasks to ensure any differences in task performance did not relate to the nature of the stimuli used; the maintenance requirement of the mental rotation task was reduced in order to isolate and emphasize the manipulation component of this task; two workload versions of each task were created in order to assess any changes provoked by domain-general executive engagement brought on by increases in difficulty.

The work presented so far suggests that maintenance is more susceptible to interference when right-lateralized extrinsic network dynamics are altered, while manipulation is more likely to suffer when intrinsic network activity is disrupted, pointing to a distinction between maintenance and manipulation. The design features outlined afford a reasonable degree of confidence that the observed results highlight an actual dissociation between maintenance and manipulation. Nevertheless, questions remain. One of these questions relates to whether the differences between maintenance and manipulation occur because the nature of the internal representation formed during rotation is different from that maintained during the delayed match-to sample task. Past research has suggested this may be the case, with different hemispheric and lateralized attentional contributions required for tasks involving an imagery component versus those requiring more “holistic” attentional modes, such as remembering a spatial location in a visual array (Tucker, Vannatta, & Rothlind, 1990). However, while past research has

observed a role of the default-mode network and left lateralized regions of the central executive network in mental rotation and visualization/imagery tasks (Markett et al., 2017), the question remains whether, and under what conditions this type of activation can be expected for the maintenance of a visual representation more generally.

In order to investigate this question, an electroencephalographic (EEG) experiment was conducted wherein I examined the electrophysiological correlates of maintenance during the delayed match-to sample task, and explored potential changes in brain dynamics instigated by an exogenous distractor. This design facilitated the investigation of: 1) predicted neural source locations that support maintenance activity, 2) inter-region communication (expressed via frequency specific modulations), and 3) how an external sensory distractor influences these network dynamics. Examining which regions are predicted sources of maintenance activity will give more insight into whether corroborating evidence points to a right-lateralized network of brain regions active during visual maintenance. While the conducted meta-analysis (Chapter 2) provides data that points to a double dissociation between the influence of arousal induced-external distraction and apprehension induced-internal distraction on storage and manipulation performance, results from the stress experiment (Chapter 3) provide converging support for the differential effect of apprehension on storage and mental rotation. To expand on this pattern of results, the aim of the current EEG study was to further examine the influence of external distraction on storage performance; in particular, to provide electrophysiological data that may illuminate network dynamics that support visual storage during external distraction. The source localization and visualization techniques employed in this experiment necessitate a minimum number of

data points that rendered the exploration of both storage and manipulation tasks unfeasible within the scope of the current design. Because of this, as well as the fact that the nature of the mental rotation task was more likely to induce muscular artifacts (e.g., saccades), the decision was made to restrict investigations to the delayed match-to sample task used previously (Chapter 3).

A key assumption of the systems neuroscience account discussed previously is that regions implicated in visual working memory exchange information during task performance. These interactions can emerge as modulations in frequency-specific EEG activity (Alivisatos & Petrides, 1997; Gao et al., 2017; Lamp, Alexander, Laycock, Crewther, & Crewther, 2016; Wolbers, Schoell, & Büchel, 2006; Zimmer, 2008) which index the routing of information and long-range coordination between brain regions (Voloh & Womelsdorf, 2016). Tracking these dynamic oscillatory changes in recorded EEG data can therefore serve as a proxy for changes in brain connectivity (Fries, 2009; van Atteveldt, Murray, Thut, & Schroeder, 2014). Furthermore, tracking the electrophysiological changes that occur in response to external distraction, while noting the working memory-related signals that are preserved despite these distractions can lend insight into the goal-directed functions that underlie visual maintenance. In particular, this investigation can determine whether activity in right-lateralized brain regions implicated in salience detection is likely to increase in response to task-irrelevant distractors, and how extrinsic and intrinsic networks interact throughout successful task completion. In order to help ground the reader, a brief explanation of EEG methodologies that support both source localization and event-related oscillatory activity follows.

### **EEG Background**

While neuroimaging methodologies such as functional magnetic resonance imaging (fMRI) offer high spatial resolution and are the usual paradigms recruited to isolate areas of brain activation, the opportunity to capitalize on electroencephalography (EEG) for source localization has increased dramatically over the last decade. Currently, many EEG researchers time-lock EEG to specific stimuli, and interpret data by measuring peak amplitudes and latency values of a single component (the event-related potential, ERP) that has been averaged over hundreds of trials. While this technique offers a wealth of important information, ERP techniques examine only a specific point in time, and thus do not capitalize on a host of other information inherent in the EEG signal, such as event-related dynamics that are not present in averaged components, and ongoing EEG processes that are only partially time-locked to the event in question (Delorme & Makeig, 2004). Within the last decade, a signal processing tool called independent component analysis (ICA), has been applied to EEG data and developed into an open source signal processing software package (EEGLab) (Delorme & Makeig, 2004).

The precise details of how ICA operates are beyond the scope of the present thesis, however a brief summary will help to inform the reader as to how this advance has given EEG systems basic imaging capabilities. Every EEG electrode records the synchronous firing of neurons oriented perpendicularly to the scalp. Many groups of neurons fire simultaneously at any given point in time, meaning that each electrode at the scalp records a mixture of all the firings occurring at any given instant. While this information can be used in ERP experiments to discover how different stimuli influence

electrical recordings, readings at the scalp level do not correlate with activity of an isolated brain region. An oft-cited analogy is the cocktail party problem in which ten people are in a room enjoying cocktails. Ten microphones are placed throughout the room recording the ambient chatter. If you were to listen to the recording of one of the microphones, you might be hard pressed to pick out one guest's narrative from the rest of the cocktail chatter. Independent component analysis, however, can separate this multivariate signal into additive components. By assuming subcomponents are statistically independent non-Gaussian signals, ICA pulls out the signals that are maximally temporally distinct, generating the ten original sources of the recorded chatter. Because the locations of the microphones are also known, ICA can also predict the locations of the original signals. In the same way, when applied to EEG data, ICA untangles the original source signals from one another (Delorme & Makeig, 2004).

After preprocessing EEG data (including filtering out electrical activity etc...), ICA is performed and data from scalp space (the original recorded data) is transformed into component data in source space (unmixed signals predicted to be associated with specific source locations in the brain). In addition to isolating components that reflect brain activity, ICA also separates non- brain related signals, such as those associated with muscle artifacts (e.g., blinks) or pulse artifacts. These components are rejected, and ICA run a second time in order to unmix non-brain activity from the EEG data. This maximizes the likelihood that resulting components reflect real signals emanating from source space. Independent component clustering is then performed, which organizes functionally equivalent independent components into groups, or clusters, based on selected features including similarity of spectral power and dipole localization. This can

be done within or across individuals, and results in a set of independent components reflecting the activity of a single predicted brain component. Clusters are maximally different from one another, and thus are associated with unique topographical locations.

In addition to examining predicted source locations of unmixed EEG data, the present study also considers signals in frequency domain (which here is more useful than the time domain given experimental aims and design). For this reason, in both channel and source space, the main parameter of interest is the event-related spectral perturbation (ERSP), which is a two-dimensional image representing the average changes in frequency power of EEG data time-locked to a particular type of event. These changes in spectral power, when examined in source space (Voloh & Womelsdorf, 2016), can characterize the spatio-temporal patterning of fast dynamic neuronal processes – processes that are not detectable with the low sampling rates of metabolically-based imaging techniques (Makeig, Debener, Onton, & Delorme, 2004). This type of analysis has led to repeated observation of frequency-specific synchronization (or desynchronization) associated with particular cognitive processes, and to the hypothesis that these changes represent a hallmark of interregional communication (Meehan, 2016). Of particular interest is that intrinsic and extrinsic networks are supported by dichotomous electrophysiological signatures, such that intrinsic network regions communicate via theta phase synchrony, while extrinsic network areas coordinate through alpha phase synchrony (Hacker et al., 2017; Meehan, 2016). These kinds of signals, therefore, can help to uncover the network dynamics supporting maintenance throughout the delayed match-to sample task employed here.

The current study uses ICA to localize the sources of brain activity during a delayed match-to sample task with concurrent exogenous distraction. This analysis will converge with previous findings to unfold a picture of the architecture and cognitive dynamics associated with visual working memory.

## Methods

### Participants and General Procedure

Twenty-four right-handed English speaking volunteers (11 female, mean age = 23 years) were recruited through Carleton's SONA system (all procedures were approved by the Carleton University Ethics Committee for Psychological Research). Upon arrival to the lab, participants read and signed a general informed consent and completed a brief set of questionnaires (10 minutes) which included self-rated alertness, length of last sleep, and time since last meal. The EEG was set up and participants completed ten blocks of two different versions of a delayed match-to sample task while ignoring task irrelevant auditory tones. The task design and EEG processing procedures are described below.

### Stimuli

**Working memory task.** All participants performed two versions of a delayed match-to sample task and were asked to judge whether a given target stimulus was identical to a previously presented stimulus. This task was identical to the delayed match-to sample task reported in Chapter 3, with the exception that the easy version contained fewer shaded cells (i.e., was easier). The memory set, generated by Python 4.0, consisted of matrix grids displaying random patterns of shaded cells. In each trial, the participant saw a task screen containing a matrix grid (5x5 grid with two shaded cells, low workload; 7x7 grid with 7 shaded cells, high workload) for 2000 ms, followed by a

delay screen of 3000 ms and finally a second matrix grid which either did or did not match the test grid. Using a Cedrus TM RB350 five-button response pad, the participant responded “yes” for a match and “no” for a non-match. The test matrix was presented for a maximum of 3000 ms or until a response was made, and was followed by a 2000 ms rest period where centered fixation cross was presented. The match-to-sample stimuli were presented in black and white in the center of a 20-inch LCD monitor (Figure 4.1). Behavioural responses were recorded on the stimulus presentation computer. Outcome measures for the match-to-sample task were response times, misses (no response within the 3-second response window), and accuracy. Easy and hard sessions were preceded by a practice block of four trials. A counterbalanced blocked method beginning with either the easy- or hard-task condition was used to present five 30-trial blocks for each workload condition.

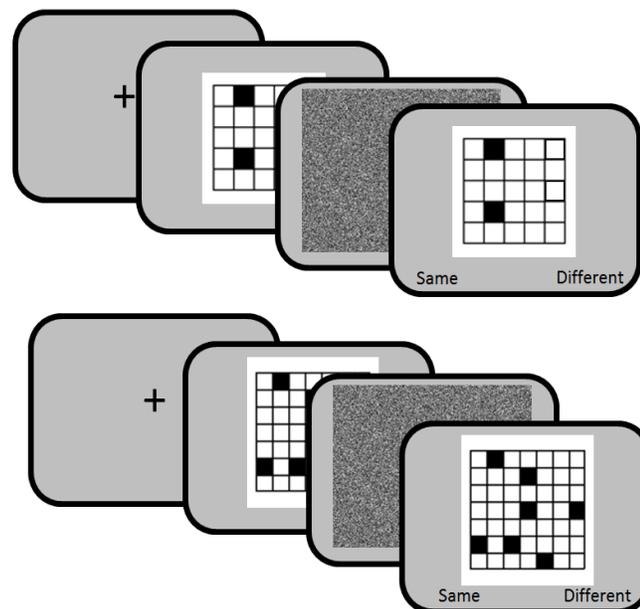


Figure 4.1. Match-to-sample stimuli and trial procedure. Top set represents the easy-task condition where two cells were filled in. Bottom set represents the hard-task condition, where seven cells were filled in.

***Task-irrelevant auditory oddball stimuli.*** In conjunction with the match-to-sample task, a task-irrelevant auditory oddball task was presented which the participants were told to ignore. Task-irrelevant tones (1000 Hz [standard] and 1500 Hz [deviant]) were presented randomly with a 1:10 ratio, with an inter-stimulus-interval of 1500 ms. Tones had a duration was 100 ms and were delivered binaurally via in-ear earphones.

### **EEG collection and preprocessing**

Data were continuously recorded from a 128 Channel HydroCel GSN electrode cap, and were amplified using a GES 250 Amplifier. Net Station 4.3.1 (Electrical Geodesics, Inc.). Data were preprocessed offline using EEGLAB, v. 13 (open source from [www.sccn.ucsd.edu/eeglab](http://www.sccn.ucsd.edu/eeglab)). Recordings were 35 to 40 minutes in length and were marked at the time of recording with event “triggers” indicating standard or deviant tone onsets in either the easy- or hard-task conditions, as well as the onset of encoding, maintenance and retrieval phases of the delayed match-to sample task.

Data was cleaned of sinusoidal artifacts using CleanLine version 1.03, band-pass filtered between 0.5 and 35 Hz, and referenced to average reference. Separate datasets were created for each of the three visual task states under investigation (encoding, maintenance, retrieval) by extracting separate epochs according to encoding, maintenance and retrieval event markers, with a 1000 ms baseline to 1400 ms post-stimulus. The remaining data were cleaned of ocular and muscular artifacts using the Automated Artifact Rejection (AAR) plugin and decomposed by logistic Infomax ICA algorithm of Bell and Sejnowski (1995). Remaining non-stereotypical noise was identified via visual inspection and removed from each dataset using inverse matrix multiplication.

Remaining stereotypical noise such as eye-blinks, lateral eye movements, and cardiac artifacts were identified by examining individual components from the ICA decomposition, and removing non-brain artifact components from the dataset.

### **EEG Analysis**

*Reliability testing.* A complication of using independent component decomposition on EEG data is that the resulting components may not be reliable, which can occur when the algorithm is not trained on enough data, for instance (Hacker et al., 2017). To safeguard against this, reliable independent components (ICs) were identified using split-half datasets as outlined previously (Groppe, Makeig, & Kutas, 2009). Even and odd trials of each experimental condition were saved as separate datasets. ICA was then performed on each half set. Subsequently, a multistep correlational template-matching process, implemented in CORRMAP v1.02 (Viola et al., 2009), was used to determine whether a “template” IC from the original dataset could be paired with an IC from both half-datasets, with the assumption that if these IC “triplets” met a correlation threshold of at least 0.85, then the IC was reliable. All ICs from the full dataset not registering homologous pairs were tagged and excluded from proceeding clustering steps. Single dipole source models were fit to the remaining IC scalp topographies using the DIPFIT2 plugin. A boundary element head model was used composed of three 3-D surfaces (skin, skull, cortex) extracted from the MNI (Montreal Neurological Institute) canonical template brain. Components were inspected to ensure that remaining component scalp maps had <15% residual variance from the best-fitting forward model scalp projection, and any remaining components were cross-referenced with the

reliability testing to corroborate their designation as artifacts and their subsequent exclusion from further analysis.

**Clustering.** Condition means were computed for component power spectra, event-related spectral perturbations, component scalp maps and equivalent dipole model locations using the time-frequency function available in EEGLAB v.13 STUDY functions (Delorme et al., 2011). While enough data was generated for comparison between low and high workload conditions within extracted maintenance epochs, this was not the case for standard versus deviant tones. Differences related to tone type were therefore not compared. Means were computed for the epoch window of -1000 ms to 14000 ms across the entire frequency range of 3-30 Hz, and then for each of the following frequency bands: delta (3-5 Hz), theta (5-7 Hz), alpha (7.5-12.5 Hz), beta (13-30 Hz).

Independent components were then semi-automatically grouped into clusters using a K-means clustering algorithm based on similarities in selected component parameters. These measures were compressed to ten principal dimensions by principal component analysis (PCA). ICs whose distance to any cluster centroid in joint measure space was larger than three standard deviations from the mean were removed from analysis. This method of clustering is not guaranteed to return the same clusters as other techniques (Groppe et al., 2009), however, the clustering distance metric used here was intentionally dominated by similarity in equivalent dipoles and event related spectral perturbation (ERSP) parameters, and adjusting it had relatively small effects on clustering. Once a set of reliable, consistent clusters was generated, dipole locations of

the centroid component were localized using Talarach Client (Version 2.4.3) (Bigdely-Shamlo, Mullen, Kreutz-Delgado, & Makeig, 2013).

Currently, there is no standardized protocol for selecting the most appropriate number of output clusters for the K-means clustering algorithm with EEG analysis. One option would be to create as many clusters as there are subjects, such that each cluster contains one component from each subject. This is an idealized scenario, given it is unlikely that all subjects will have equivalent independent components that cluster symmetrically into a uniform matrix. Nevertheless, it does offer some guidance: in order to obtain a set of clusters that adequately captures the neural dynamics of the group as a whole throughout the experimental task performed here, each cluster should have a high percentage of subjects contributing to it (representivity), and the total number of subjects contributing with only one component to a given cluster (unicity) should be high. Following exemplary research (Lancaster et al., 2000) and considering the size reduction in parent cluster components after reliability testing, a representivity criterion superior or equal to 0.5, and a unicity criterion superior or equal to 0.3 were selected.

### ***Analysis.***

***Channel space.*** Channel level data was investigated for exploratory and comparative purposes; however, emphasis is not placed on these results since data features of interest are not actually generated in the scalp, but rather the brain itself, and under favorable circumstances independent component filtering allows isolation of the separate brain source activities, rather than their correlated mixtures recorded at scalp electrodes. For the current analysis, I examined the following channels of the 128 Channel HydroCel GSN electrode cap: F3, F4, F7, F8, Fz, C3, C4, T3, T4, T5, T6, P3,

P4, Pz, O1, O2, Oz (Figure 4.2). As mentioned (Introduction), the primary functional feature evaluated was the mean event-related spectral perturbation (ERSP) time locked to auditory tones presented within the maintenance phase. To calculate ERSPs, the Morlet wavelet decomposition was applied as implemented in EEGLAB *newtimef()* to the channel data. Power was calculated for 100 log-spaced frequencies ranging from 3 to 125 Hz, and along 200 linearly spaced time bins.

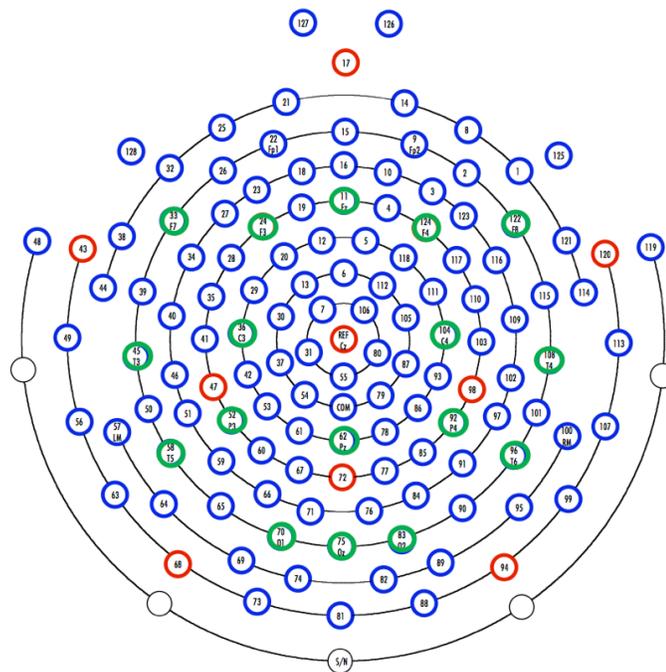


Figure 4.2. Sensor locations. An EGI™ HydroCel Geodesic Sensor Net 128 channel map. Green circles represent analyzed sensor locations. The electrode locations for 68, 73, 88 and 94 were unused. Retrieved from [ftp://ftp.egi.com/pub/support/Documents/net\\_layouts/hcgsn\\_128.pdf](ftp://ftp.egi.com/pub/support/Documents/net_layouts/hcgsn_128.pdf)

**Source space.** Group comparisons were conducted on spectral measures extracted from cluster independent components (ICs) for each of the following spectral bands: delta (3-5 Hz) theta (5-7 Hz), alpha (7.5-12.5 Hz), beta (13-30 Hz). These spectral bands were analyzed separately using repeated-measures ANOVA, and p-values were computed at

every time/frequency point to compare event-related spectral power changes in the low and high workload conditions.

## Results

### Behavioural analyses

Performance outcomes confirmed the hard version of the delayed match-to sample task was more difficult than the easy version of the task. Participants were significantly less accurate  $t(23) = 15.88, p < .001$  and took significantly longer  $t(23) = 5.86, p < .001$  in the hard condition than the easy condition.

### EEG data

The average number of time points decomposed for each subject was 98 172 (+/- 13578), which is above the minimum recommended number of data points for finding stable components prescribed by the formula  $3 \times Nx^2$  (where N is the number of channels) (Delorme, n.d.).

**Channel level.** Permutation statistics of the channels of interest revealed a working-memory related increase in theta power along the midline channels and extending into the right hemisphere frontally (Figure 4.3). Increased alpha power was also evident in right parietal channels in the high-workload condition, with peak power occurring in Pz (Figure 4.4). Increased beta power was observed across a range of channels with scalp topographies showing a right-lateralized distribution, with peak power in C4 (Figure 4.5).

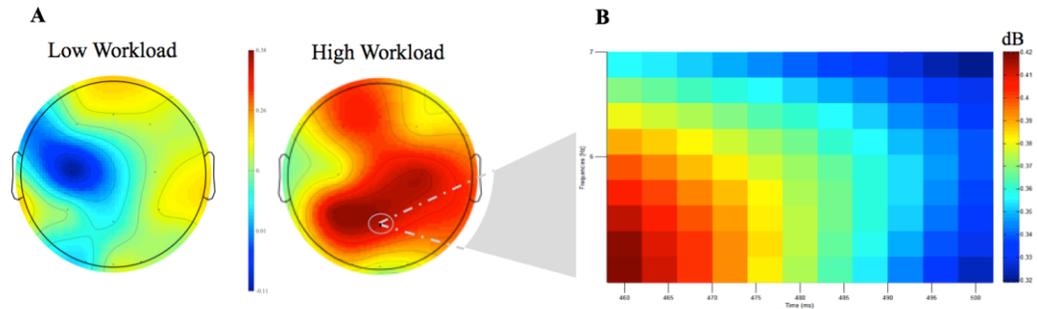


Figure 4.3. Theta band results in channel space. Scalp topographies associated with Low and High Workload conditions in the theta band. Circular schematics represent the scalp surface, with small black dots indicative of electrode sensors. The middle colour bar indicates dB level of theta band activity. (Panel A). Maximum theta power was observed proximal to the Pz channel, which was selected as a representative electrode to illustrate event-related changes in theta spectral power (ERSP) (from pre-stimulus baseline). The ERSP plot depicted in panel B is masked for significance by the critical  $p$  value (0.05) after correction for false discovery rate. Right-hand colour bar indicates dB level of theta band activity, time is displayed on x axis (Panel B).

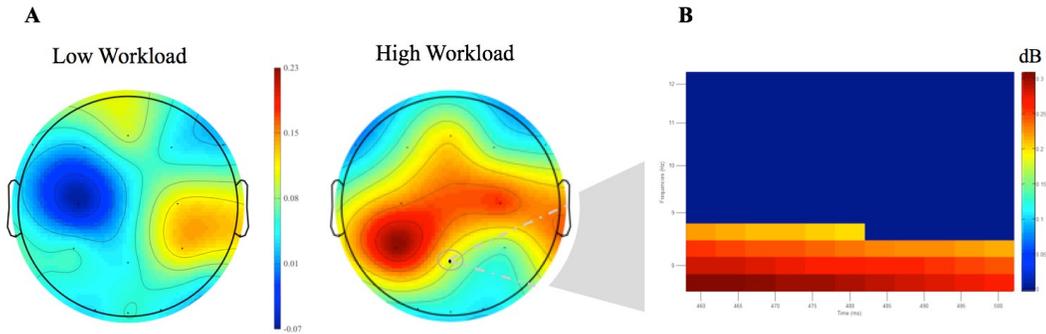


Figure 4.4. Scalp topography in alpha band for Low and High Workload conditions (Panel A). Mean event-related changes in spectral power (from pre-stimulus baseline) in the alpha band occurring in Pz channel, masked for significance by the critical  $p$  value (0.05) after correction for the false discovery rate (Panel B).

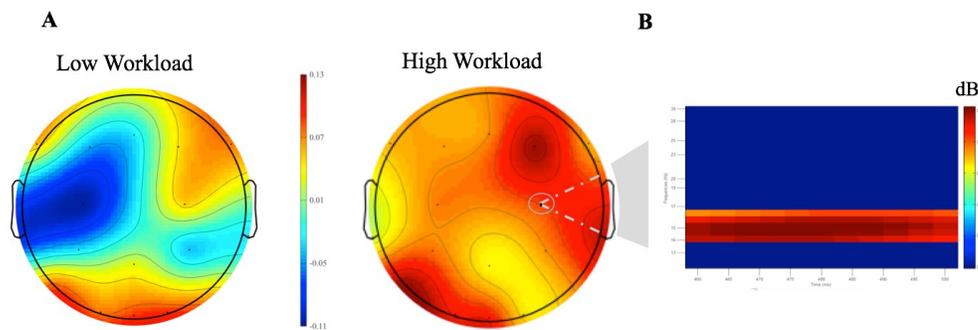


Figure 4.5. Scalp topography in beta band for Low and High Workload conditions (Panel A). Mean event-related changes in spectral power (from pre-stimulus baseline) in the beta band occurring in C4 channel, masked for significance by the critical  $p$  value (0.05) after correction for the false discovery rate (Panel B).

### *Source level.*

***Dipole localization.*** Clustering of epoched data from the maintenance phase revealed several consistent right- and left-hemispheric clusters. In the right hemisphere, five clusters passed selection criteria. Coordinates of cluster centroids placed two of the five clusters in the frontal cortex (Figure 4.6). One cluster was centered near Brodmann Area (BA) 11 (MNI:  $x = 9$  mm,  $y = 46$  mm,  $z = -24$  mm). Hierarchical clustering applied to the second frontal parent cluster revealed three subclusters: one was localized near the inferior frontal gyrus (near BA 10/47) (MNI:  $x = 31$  mm,  $y = 60$  mm,  $z = -7$  mm); the second was located proximal to the dorsolateral prefrontal cortex, near BA 9/46 (MNI:  $x = 47$  mm,  $y = 43$  mm,  $z = 21$  mm); the third was localized near the superior frontal gyrus near BA 8/6 (MNI:  $x = 41$  mm,  $y = 4$  mm,  $z = 38$  mm). Of the three posterior clusters (Figure 4.7), one was located in the parietal lobe, one in the temporal lobe and one in the occipital lobe. Hierarchical clustering of parietal and temporal clusters revealed two subclusters in the parietal lobe, one superiorly and near BA 7 (MNI:  $x = 20$  mm,  $y = -76$  mm,  $z = 42$  mm) and one inferiorly and near BA39/40 (MNI:  $x = 58$  mm,  $y = -57$  mm,  $z$

= 31 mm), and two subclusters in the temporal lobe, with one centered superiorly near BA 22/42 (MNI:  $x = 64$  mm,  $y = -7$  mm,  $z = -3$  mm) and one inferiorly near BA 20/21/37 (MNI:  $x = 45$  mm,  $y = -20$  mm,  $z = -23$  mm). The final occipital cluster was located near BA 17/18/19 (MNI:  $x = 29$  mm,  $y = -83$  mm,  $z = -3$  mm). Although they did not pass representativity nor unicity criteria, it is worth noting that two smaller clusters were also revealed near the anterior cingulate cortex (MNI:  $x = -6$  mm,  $y = 23$  mm,  $z = 14$  mm) and posterior cingulate cortex (MNI:  $x = 9$  mm,  $y = -38$  mm,  $z = 24$  mm).

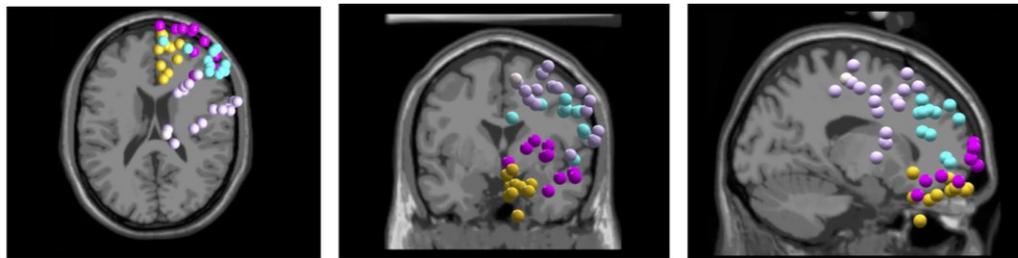


Figure 4.6. Right-hemispheric frontal clusters. Top (left panel), coronal (middle panel) and sagittal (right panel) views of the four consistent right-hemispheric frontal clusters found during maintenance. Spheres represent equivalent dipole locations of reliable independent components. Magenta denotes the ventral frontal cluster (BA 10/47); orange is the inferior frontal cluster near BA11, blue is the right dorsolateral prefrontal cortex cluster (BA 9/46) and purple is the superior frontal cluster (BA 8/6).

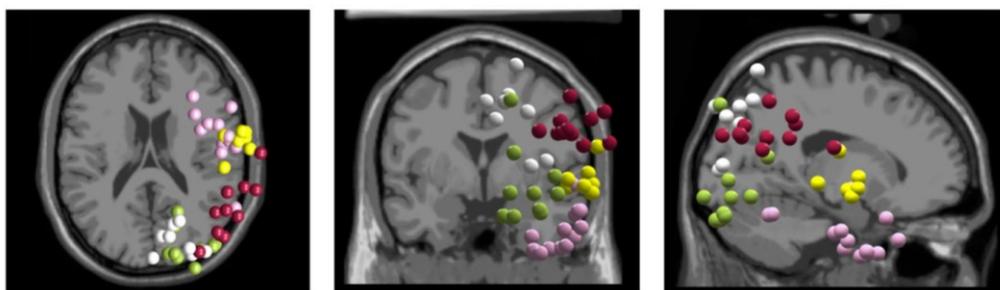


Figure 4.7. Right-hemispheric posterior clusters. Top (left panel), coronal (middle panel) and sagittal (right panel) views of right posterior clusters found during maintenance phase. Spheres represent equivalent dipole locations of reliable independent components. Light pink denotes the inferior temporal cluster (BA 20/21/37); yellow the superior temporal cluster (BA22/42), red is the inferior parietal cluster (BA39/40), white is the superior parietal cluster (BA 7), and green is the occipital cluster (BA 17/18/19).

Source localization also revealed five reliable clusters in the left hemisphere. Frontally, two clusters were found with centroids near BA11 (MNI:  $x = -9$  mm,  $y = 41$  mm,  $z = -24$  mm) and the inferior frontal gyrus (BA 10/47) (MNI:  $x = -38$  mm,  $y = 52$  mm,  $z = 0$  mm) (Figure 4.8). Clusters were also observed centered in inferior parietal cortex (BA 39/40) (MNI:  $x = -44$  mm,  $y = -45$  mm,  $z = 43$  mm), inferior temporal cortex (BA 21/30/37) (MNI:  $x = -65$  mm,  $y = -20$  mm,  $z = -10$  mm) and occipital lobe (BA 18/19) (MNI:  $x = -28$  mm,  $y = -80$  mm,  $z = 3$  mm). (Figure 4.9).

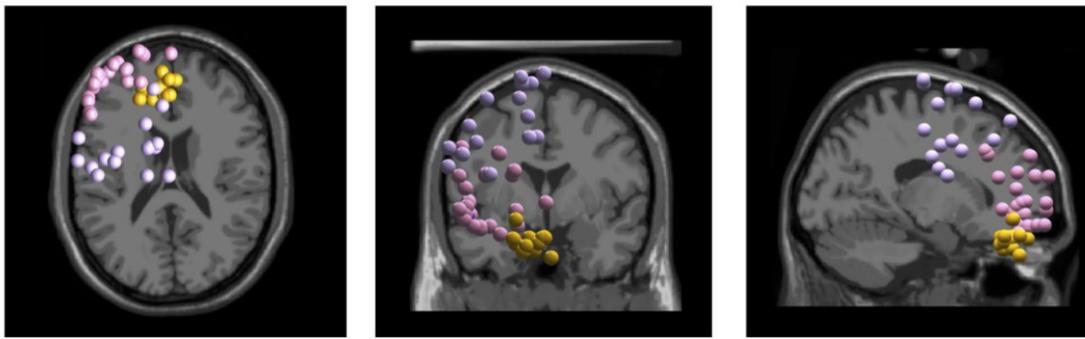


Figure 4.8. Left-hemispheric frontal clusters. Top (left panel), coronal (middle panel) and sagittal (right panel) views of three left-hemispheric frontal clusters found during maintenance phase. Spheres represent equivalent dipole locations of reliable independent components. Pink denotes the ventral cluster proximal to BA 10/47; orange is the inferior frontal cluster near BA11 and purple is the superior frontal cluster (BA 8/6).

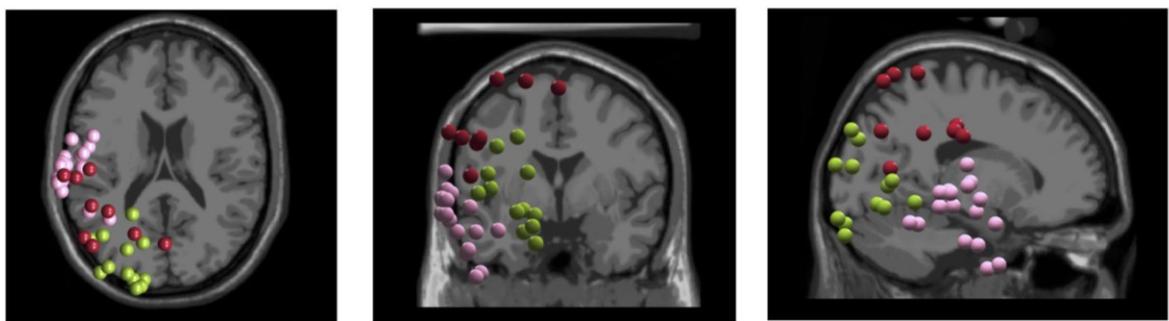


Figure 4.9. Left-hemispheric posterior clusters. Top (left panel), coronal (middle panel) and sagittal (right panel) views of the three left-hemispheric posterior clusters found during maintenance phase. Spheres represent equivalent dipole locations of reliable independent components. Light pink denotes temporal cluster (BA 20/21/37); red is the parietal cluster (BA39/40) and green is the occipital cluster (BA 18/19)

***Load effects.***

Alpha. The high workload condition was associated with a significant alpha synchronization in the right inferior temporal (mean power = 0.0420 dB) and bilateral occipital (mean power = 0.0144 dB) clusters (Figure 4.10), as well as an increase in event-related alpha desynchronization for right dorsolateral (mean power = 0.0560 dB) and right superior frontal (mean power = 0.0902 dB) clusters (Figure 4.11).

Theta. Load-related increases in theta synchronization were observed in the right inferior frontal cluster (located near BA10/47) (mean power = 0.5061 dB) and anterior cingulate cluster (Figure 4.12).

Delta. The superior parietal cluster near BA 7 was associated with a significant increase in delta synchronization under high-workload conditions (mean power = 0.1141 dB) (Figure 4.13).

Beta. A Load-related increase in beta synchronization was observed in the right inferior parietal cluster. (mean power = 0.1067) (Figure 4.14).

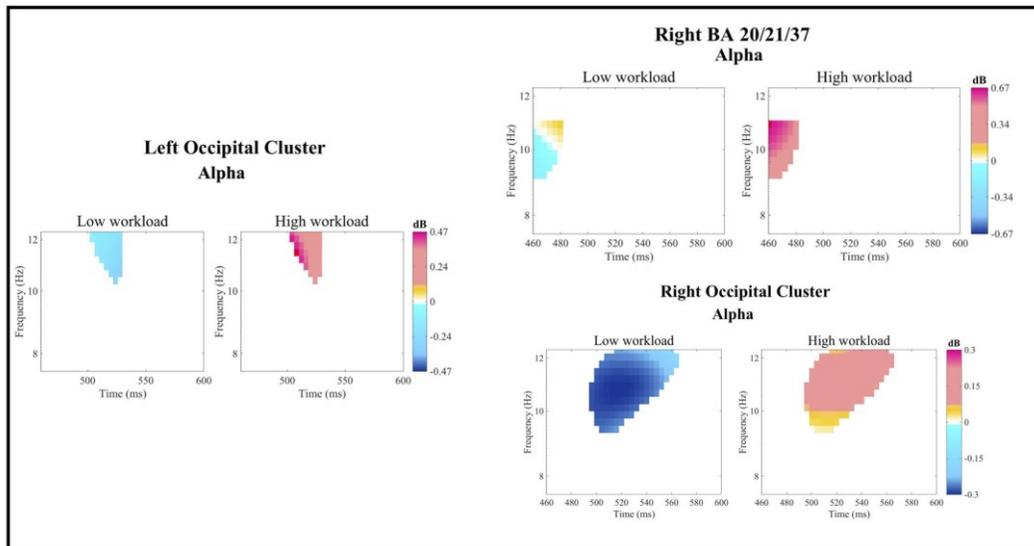


Figure 4.10. Clusters exhibiting load-related alpha synchronization. Plots are masked for significance by the critical  $p$  value such that white regions are areas in which event-related spectral perturbation was not significant ( $p > 0.01$ ). Cluster names are indicated with axes titles, and Low and High workload conditions are shown with left- and right-sided ERSP plots, respectively. Colour bars to the right of each set of panels denote spectral power (dB), with cool colours reflecting a desynchronization in spectral power, and warm colours reflecting a synchronization (positive) modulation. Time is denoted by the x-axis.

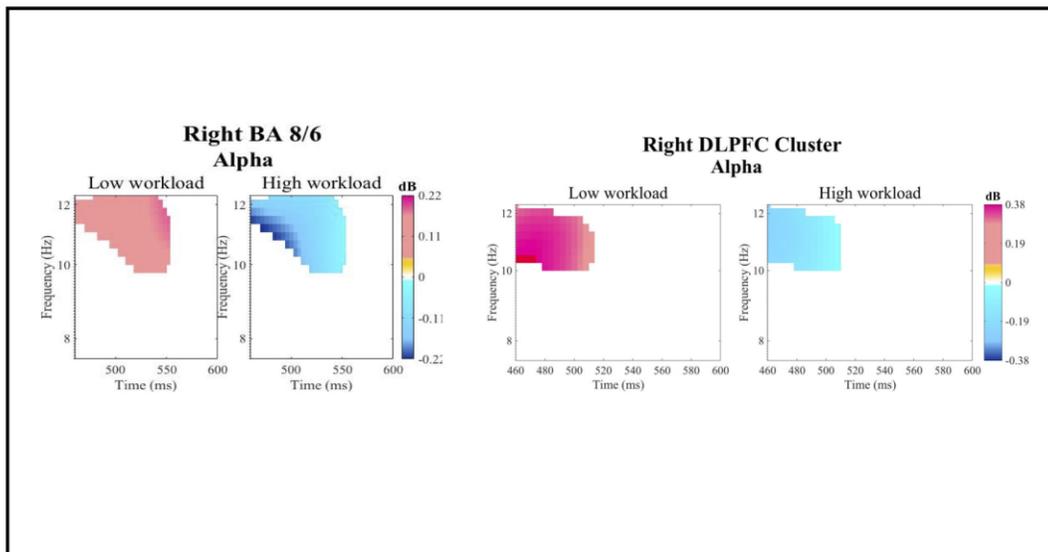


Figure 4.11. Clusters exhibiting load-related alpha desynchronization. Plots are masked for significance by the critical  $p$  value such that white regions are areas in which event-related spectral perturbation was not significant ( $p > 0.01$ ).

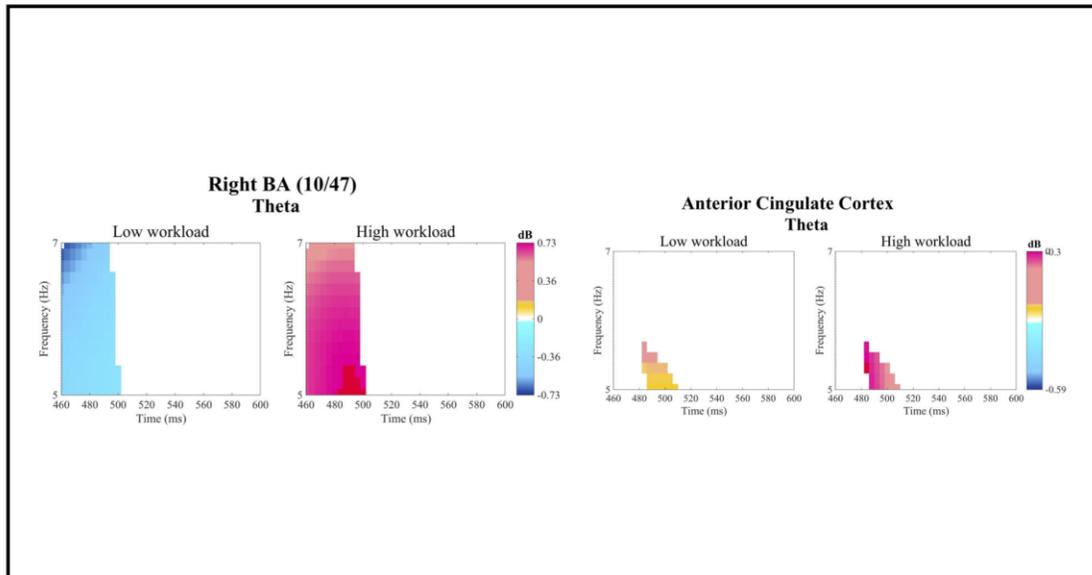


Figure 4.12. Clusters exhibiting load-related theta synchronization. Plots are masked for significance by the critical  $p$  value such that white regions are areas in which event-related spectral perturbation was not significant ( $p > 0.01$ ).

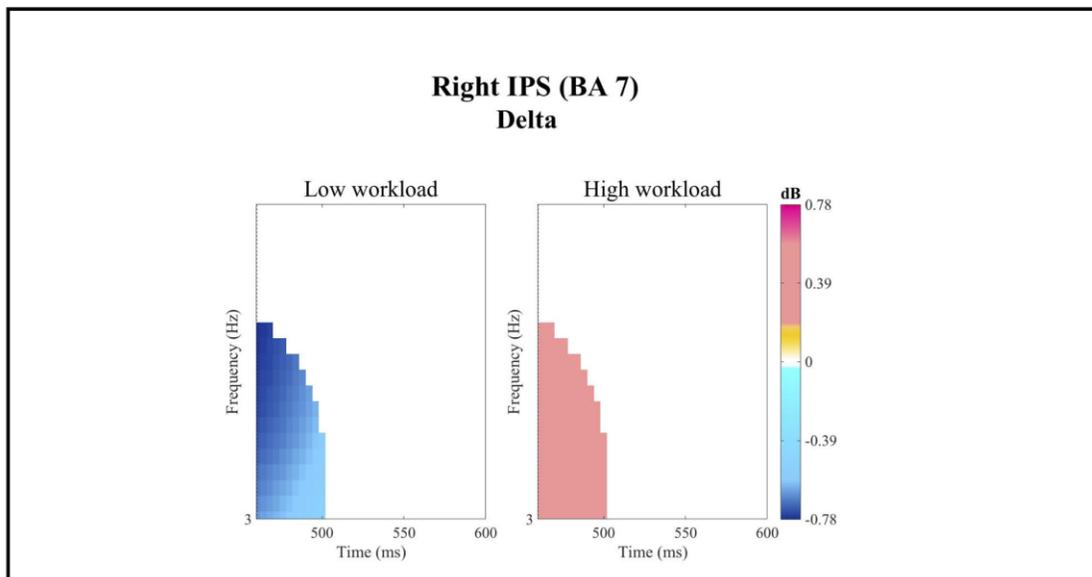


Figure 4.13. Right intraparietal sulcus (IPS) cluster exhibiting load-related delta synchronization. Plots are masked for significance by the critical  $p$  value such that white regions are areas in which event-related spectral perturbation was not significant ( $p > 0.01$ ).

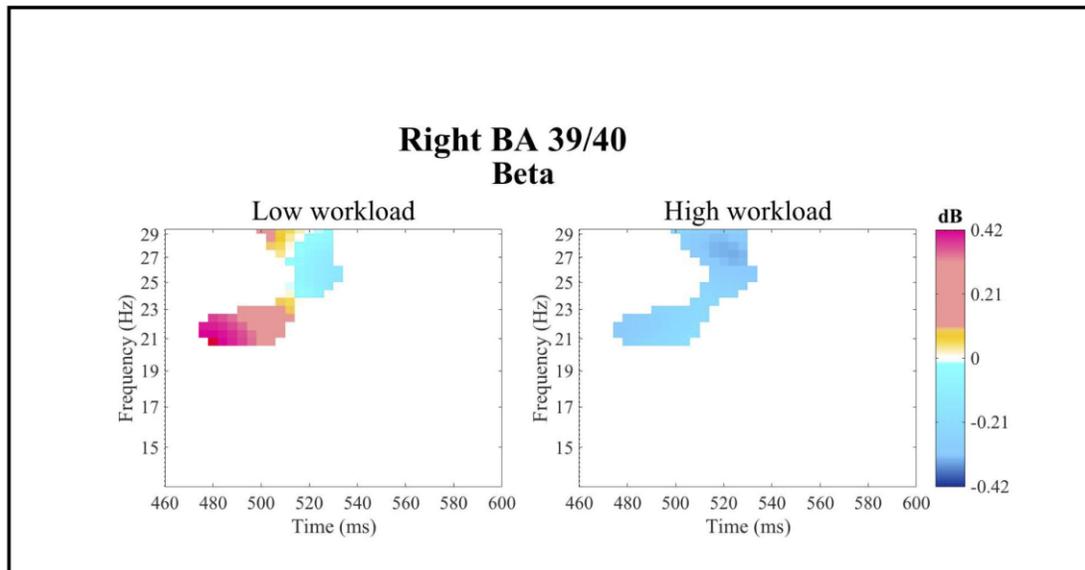


Figure 4.14. Right temporoparietal junction (TPJ) cluster exhibiting load-related beta desynchronization. Plots are masked for significance by the critical  $p$  value such that white regions are areas in which event-related spectral perturbation was not significant ( $p > 0.01$ ).

## Discussion

The current study used electroencephalographic (EEG) methodologies to examine maintenance of visual information during concurrent exogenous auditory distraction. Several patterns of activity exist in the current data that will be briefly discussed in order to infer the causal source and the functional significance of the observed changes.

At the channel level, working-memory related increases were observed in theta power along frontal midline channels extending into the right hemisphere (Figure 4.3), and increased alpha power in right parietal channels in the high-workload condition (Figure 4.4). These findings are consistent with a number of recent studies. Increased frontal midline theta has been associated with “task-orientedness”, working memory and mental effort (Onton et al., 2005), while increased posterior alpha during maintenance has been suggested to reflect active inhibition of these areas from reorienting to

irrelevant information during storage (Lenartowicz et al., 2014; Pavlov & Kotchoubey, 2017; van Driel, Günseli, Meeter, & Olivers, 2017). Although consistent with previous findings, channel level activity on its own is not overly illuminating because data features of interest are not actually generated in the scalp, but rather the brain itself. For this reason, independent component analysis was performed in order to separate brain source activity from correlated mixtures recorded at scalp electrodes.

Source level analyses revealed maintenance-related activity in several key clusters throughout right and left hemispheres. The discussion of these clusters begins with a summary of predicted sources according to an intrinsic/extrinsic network classification scheme. A discussion of observed oscillatory modulations within these clusters as well as the network implications of these findings will then follow. In the right hemisphere, independent components were separated into two main groups with one cluster localized near the inferior frontal gyrus (centroid proximal to Brodmann Area (BA) 11). The second parent cluster was separated via hierarchical clustering into three subclusters with centroids located near the right dorsolateral prefrontal cortex, right inferior frontal gyrus (near BA 10/47) and right superior frontal gyrus (centroid proximal to BA 8/6, near the frontal eye fields). A right-parietal parent cluster was separated into a superior subcluster (centroid proximal to BA 7, near the intraparietal sulcus) and an inferior subcluster (centroid proximal to BA 22/42, near the temporoparietal junction). Clustering also revealed a parent cluster located in the temporal lobe that was divided into a superior temporal subcluster (near BA 22/42) and an inferior temporal cluster (near BA 20/21/37). Similar clusters were revealed in the left hemisphere, with the exception that no dorsolateral prefrontal, superior parietal nor superior temporal clusters emerged.

Intriguingly, several of these regions belong to two putative systems discussed in the previous chapters – one that engages with the internal environment and one that interfaces with the external world (Fox et al., 2005; Hacker et al., 2013). The purported categorization of relevant clusters is summarized (Table 4.1). To review, although terminology varies across research groups, and inclusion criteria is not always identical, two groups of component subsystems have emerged that fall under a proposed hierarchical subdivision between internally- and externally- oriented cognition (Doucet et al., 2011; Hacker et al., 2017; Meehan, 2016; Spreng, 2012; Zabelina & Andrews-Hanna, 2016). The network supporting internally-oriented cognition, also known as the “intrinsic” system (Doucet et al., 2011; Hacker et al., 2017), includes the default mode network (DMN). The default mode network has traditionally been associated with task-negative and self-referential activity (Andrews-Hanna, 2012; Fox et al., 2005) but is also recruited by episodic memory (Buckner et al., 2008), and the fronto-parietal control network (FPCN), which is recruited by executive control tasks (Dosenbach et al., 2006; Fedorenko et al., 2013) and can be divided into central-executive and cingulo-opercular subsystems. According to these conventions, three of the clusters found here belong to this broader intrinsic network based on equivalent dipole locations: a right dorsolateral prefrontal (dlPFC) cluster as well as right and left inferior frontal clusters (BA 10/47). While the right dlPFC belongs to the central-executive module of the FPCN, the inferior frontal clusters may represent more general regions of the medial PFC, a suggested hub of the default mode network core. As mentioned (Results), a smaller cluster was also observed that was localized near the anterior cingulate cortex. This is a region of the limbic system which is sometimes considered part of the default mode network (Zabelina

& Andrews-Hanna, 2016). The second, “extrinsic” system is often defined in terms of its “anti-default mode network” characteristics in order to emphasize its role in task-positive activity, and consists of the dorsal attention network, which mediates top-down control of spatial attention (Corbetta & Shulman, 2002), the ventral attention network, which is involved in reorienting and overlaps with the salience network, the visual network and the somatomotor network. According to this metric, at least seven clusters obtained in the current experiment belong here: one left and one right occipital cluster (belonging to the visual network), one right and one left superior frontal cluster (near BA 8/6, or the frontal eye fields, which are part of the dorsal attention network), a right superior parietal cluster (near Brodmann areas 7, which is also part of the dorsal attention network) and one left and one right inferior parietal cluster (near BA 39/40, close to the temporo-parietal junction, which belongs to the ventral attention network).

Table 4.1: Network classification summary of obtained clusters

Network	Cluster	Brodmann Area	Hemisphere	Centroid MNI	Subsystem
Extrinsic	Superior frontal gyrus	8/6	Right	41,4,38	Dorsal attention network
	Intraparietal sulcus	7	Right	20,-76,42	Dorsal attention network
	Temporoparietal junction	39/40	Right	58,-57,31	Ventral attention network
	Temporoparietal junction	39/40	Left	-44,-45,43	Ventral attention network
	Inferior temporal lobe	20/21/37	Right	45, -20,-23	Visual network
	Inferior temporal lobe	20/21/37	Left	-65, -20,-10	Visual network
	Occipital	17/18/19	Right	29, -83, -3	Visual network
	Occipital	18/19	Left	-28,-80,3	Visual network
	Intrinsic	Inferior frontal gyrus	10/47	Right	31, 60, -7
Inferior frontal gyrus		10/47	Left	-38, 52, 0	Default mode network
Dorsolateral prefrontal cortex		9/46	Right	47,43,21	Frontoparietal control network

Note: Coordinates from MNI (Montreal Neurological Institute) canonical template brain

Clusters were defined by equivalent dipole similarity and event-related spectral perturbation (ERSP) parameters. Independent components within each cluster are therefore not only relatively homogenous in terms of their predicted locations, but also in terms of event-related changes in oscillatory activity. In addition to indexing neural activity, such oscillatory activity can serve as a proxy for changes in brain connectivity, as discussed (Introduction). An exploration of observed spectral changes can therefore lend insight into how brain activity was coordinated in response to experimental task demands, which includes the requirement to sustain maintenance of visual information in the presence of external auditory distraction. Because working memory-related changes in alpha and theta band power have received relatively more attention than other frequencies, the exploration begins with these spectral bands.

### **Alpha**

Research has generally associated increased alpha power in a particular area with decreased blood oxygen level dependent (BOLD) activity. This observation, paired with the finding that alpha power tends to increase in areas not involved in task performance, has led to the conventional view that alpha synchronization indexes cognitive inactivity (i.e., ‘cortical idling’ (Adrian & Matthews, 1934)) (Cooper, Croft, Dominey, Burgess, & Gruzelier, 2003). However, more recent research suggests that alpha modulations increase signal to noise ratios within the cortex by inhibiting processes that conflict with goal-directed activity (Klimesch, Doppelmayr, Röhme, Pöllhuber, & Stadler, 2000). In particular, alpha synchronization may mark inhibited activity that would otherwise reorient cognitive focus to distracting and irrelevant information (Cooper et al., 2003), while alpha desynchronization may indicate network activation. In line with this, load-

related increases in alpha synchronization were observed in both left and right occipital clusters, consistent with a purported sensory inhibition mechanism that reduces external visual interference during maintenance (Lenartowicz et al., 2014; Pavlov & Kotchoubey, 2017; van Driel et al., 2017). This load-related alpha suppression was also seen in the right inferior temporal cortex, which has also been implicated in visual processing (Ranganath, 2006). However, this latter result should be interpreted with caution since the inferior temporal cluster examined in the current experiment combined a relatively broad group of independent components spaced throughout Brodmann areas 20, 21 and 37 (Figure 4.10) – regions implicated in a variety of cognitive processes not restricted to visual processing alone. These findings are corroborated by other research that documents an alpha reduction in visual sensory areas when attention is directed to internal representations, such as during imagery and retention of representations in working memory (e.g., Wang et al., 2015).

While alpha modulation may certainly index region-specific changes in cortical activity, it is also currently accepted that slow-wave oscillatory activity in the theta-alpha range coordinates excitability *across* brain regions (Bahramisharif et al., 2013; Burke et al., 2015; Ekstrom and Watrous, 2014; Jensen et al., 2014; van der Meij et al., 2012). This coordinating activity is thought to link sensory, motor, control and memory modules according to specific task demands (Fries, 2005; Helfrich and Knight, 2016). Of particular interest is the fact that recent research has suggested extrinsic and intrinsic networks are supported by dichotomous electrophysiological signatures, such that extrinsic network regions communicate via alpha phase synchrony, while intrinsic network areas coordinate through theta phase synchrony (Hacker et al., 2017).

In the current experiment, alpha modulation was observed in key areas of the extrinsic network: a right superior frontal cluster (Figure 4.11) with predicted source location near the frontal eye fields (a region of the dorsal attention network), as well as left and right occipital clusters. Alpha desynchronization in the right frontal eye field cluster occurs with a slightly earlier onset than the alpha synchronization in occipital regions, possibly suggesting that this area of the dorsal attention network plays a role in inhibiting sensory visual activity during the maintenance phase of the delayed match-to-sample task. Interestingly, increased alpha was also observed in the right dlPFC cluster. In some cases, the right dlPFC is classified as part of the frontoparietal control network (FPCN) (e.g., Doucet et al., 2011; Hacker et al., 2013; Lückmann, Jacobs, & Sack, 2014), while in others it is considered part of the dorsal attention network (e.g., Spreng, Stevens, Chamberlain, Gilmore, & Schacter, 2010). In any event, it seems clear that these two systems overlap (Spreng et al., 2010), and that regions of the FPCN can couple flexibly with both regions of the ventral attention and dorsal attention networks, acting as a sort of cortical mediator that directs activity according to task needs. The ventral attention and FPC networks are suggested to work together in both cooperative and antagonistic manners depending on task demands (Young, 2017). Given that ventral and dorsal attention networks are usually anti-correlated (e.g., Corbetta & Shulman, 2002), that ventral attention network activity is suppressed during my experimental task (as will be discussed) and that alpha activity in the frontal eye fields and the right dlPFC are known to couple, it is likely that the right dlPFC cluster is involved in top-down control throughout the maintenance phase of my task. However, it should also be noted that this cluster contains a small representative set of components relative to other clusters that

emerged from the analyses presented here, which could reflect individual differences in processing. For example, individuals with lower imagery abilities may be less able to rely on the same network dynamics that are adequate for other individuals, and instead may need to invoke FPCN regions for controlled strategy use.

### **Theta**

In addition to the alpha modulation discussed, modulation in theta power was also observed at the source level. Increased load-related theta power was localized to clusters in the medial prefrontal cortex (the right inferior frontal cluster near BA 10/47, and a smaller cluster with components localized to the anterior cingulate cortex) (Figure 4.12). This is consistent with several other studies that have associated increased theta-range activity observed during working memory with the medial prefrontal cortex including the inferior frontal gyrus and anterior cingulate (Harmony, 2013; Hsieh & Ranganath, 2014; Kaplan et al., 2017; Michels et al., 2010; Scheeringa et al., 2009). These findings are also consistent given that the clusters displaying theta modulation are also putative members of the core default mode network, a subsystem of the intrinsic network which is believed to coordinate its activity via theta synchronization. The exact significance of this theta modulation, however, is unclear given engagement of intrinsic system regions has been variably reported as both enhancing and suppressing theta oscillations (Hacker et al., 2017). On one hand, theta is documented to correlate negatively with blood oxygen level dependent (BOLD) activity (Scheeringa et al., 2009); on the other, theta phase synchronization has been recently suggested to play a role in the coordination of attentional functions (Sebastian et al., 2016). While it would make sense that default mode regions would be less active as working memory requirements increase, some

researchers have suggested a role for the inferior frontal gyrus (BA 10/47) in the disengagement of attention that has been drawn reflexively (and therefore as a sort of post-processing of exogenous attention) (Lückmann et al., 2014; Snyder & Chatterjee, 2006), and this region has been put forth as a potential site that mediates the interaction between ventral and dorsal attention networks during stimulus-based reorienting (e.g., Corbetta, Patel, & Shulman, 2008). It may be the case, therefore, that this region is involved in suppression of any reorienting tendencies tempted by the task-irrelevant auditory tones presented concurrently to the primary goal of visual maintenance. These results warrant further investigation.

### **Delta**

Load-related modulation was also observed in the right superior parietal cluster (near BA 7), consistent with other reports of right-lateralized involvement of the intraparietal sulcus (IPS) in visual working memory tasks, which is thought to participate alongside a larger distributed network (Dores et al., 2017; Yamanaka, Yamagata, Tomioka, Kawasaki, & Mimura, 2010). As mentioned, it is clear that visual working memory involves a two-way interaction between perceptual input from the outside world and internal representations of this world. Exactly where, and how this transfer of information occurs is still unclear. The intraparietal sulcus is a candidate for this coordination (Sestieri, Shulman, & Corbetta, 2017). This posterior parietal area has been associated with a range of cognitive functions, including perceptual and visual attention, top-down modulation to sensory regions and memory retrieval, and perhaps not surprisingly, its suggested involvement extends not only to the dorsal attention network (Corbetta et al., 2008), but also frontoparietal (Sestieri, Corbetta, Spadone, Romani, &

Shulman, 2014; Yeo et al., 2011) and default mode networks (Raichle et al., 2001; Shulman et al., 1997). The IPS is a suggested zone of integration for visual attentional control, and its anatomical position and functional topography are consistent with a potential role in mediating endogenous attention (Meehan, 2016). It has been suggested to represent a central “hub” of the which flexibly couples with other networks in the service of goal-directed behaviour (Dosenbach et al., 2007; Spreng, Sepulcre, Turner, Stevens, & Schacter, 2013). A functional outcome of this node is the ability to transition between internally- and externally- directed attention (Cona, Marino, & Bisiacchi, 2017), which is a prerequisite for many visual memory operations such as the delayed match-to sample task used in this experiment.

Within the right IPS cluster, a load-related increase in delta power was observed (Figure 4.13). While delta power has conventionally been associated with deep sleep, and has received less relative attention than theta and alpha bands, it is important to note that research has argued for a functional distinction between slow-wave sleep and waking delta (Murphy et al., 2009). The fact that delta activity is characteristic of a state in which interneurons and thalamocortical inputs are inactive has led to the suggested role of delta as inhibiting sensory areas that interfere with internal concentration during mental tasks. For example, researchers examining oscillatory activity associated with mental arithmetic observed an increase in delta power in Broca’s area as well as left parietotemporal cortices during mental arithmetic (Harmony et al., 1999), which was later interpreted as reflecting increased internal concentration during subvocal speech necessary for task completion (Harmony, 2013). While decreased delta activity has been associated with attention to the external environment, increased delta power has been

observed during internal processing. Slow oscillatory activity (including delta (Klados et al., 2013)) is thought to reflect the coordination of global regions involved in intrinsic activity. In light of this, the increased delta power observed is consistent with a role for the right IPS as a central hub that integrates between external and internal information, and allows for the maintenance of internal representation as required by my experimental task.

### **Beta**

Decreased beta power was observed with increased working memory load in the right inferior parietal cluster (near the temporoparietal junction (TPJ)) (Figure 4.14). This region is part of the ventral attention network, and is activated upon detection of unexpected stimuli. These results are consistent with previous reports of event-related desynchronization in beta power during increased working memory performance (Li Hegner, Lutzenberger, Leiberg, & Braun, 2007), which has been attributed to potential deactivation of the right TPJ leading to decreased distraction to external stimuli. Initially, the TPJ was suggested to act as a circuit breaker for the dorsal attention network (Corbetta & Shulman, 2002); however, more recently researchers have found this difficult to accept given regions of the dorsal attention network are seen to activate earlier than the TPJ (Vossel, Geng, & Fink, 2014). Instead, some researchers suggest a role for the intraparietal sulcus or frontal eye fields in TPJ suppression (Vossel et al., 2014), while others point to a role for the right dlPFC. Interestingly, clinical research documents an association between a chronically hypoactive right dlPFC and over-activation of the ventral attention/salience network, which is thought to contribute to the inappropriate assignment of salience to innocuous stimuli, leading to delirium in some individuals

(Young, 2017). Transcranial magnetic stimulation studies have also shown a causal role for the dlPFC in successful maintenance during distraction, bolstering its possible role in ventral attention/saliency network suppression (Feredoes, Heinen, Weiskopf, Ruff, & Driver, 2011). While the timing of such network dynamics cannot be confirmed based on the analyses performed here, the onset of beta modulation in the TPJ cluster does occur slightly later than the alpha modulation of both the right frontal eye field cluster and the right dlPFC cluster, suggesting that these regions may contribute to ventral attention/saliency network suppression.

### **Summary**

Overall, the present results provide support for a distributed network view of visual working memory, which, in contrast to locationist views, emphasizes the complex interplay between top-down and bottom-up attentional interactions during visual working memory task performance. The predicted locations of the resulting clusters are consistent with a right-lateralized network that supports working memory maintenance. The observed load-related spectral modulations within these clusters point to an important interplay between intrinsic and extrinsic networks. Several results in particular support findings presented earlier (Chapters 2, 3) and will be discussed briefly below.

The load-related decrease in beta power observed in the right temporoparietal junction (TPJ) cluster (which I interpreted as reflecting decreased TPJ activity) is consistent with my earlier suggestion that ventral attention network suppression is important for successful task completion on tasks requiring top-down control of attention to external stimuli (as well as to their internal representations). It is also consistent with the idea that an increase in right-lateralized ventral attention network activity, which

occurs during threat (as well as with the “physical”-type stressors examined in the presented meta-analysis (Chapter 2)), can alter dynamics that otherwise support maintenance tasks, leading to impaired performance such as that documented in the meta-analysis. Recent evidence supports the idea that the right intraparietal sulcus (IPS) expresses both elevated neural activity as well as global brain connectivity (including with regions of the ventral attention network) during threat (Balderston et al., 2017). This is taken to indicate that states of threat-induced hyper-orienting impair performance on working memory tasks by hijacking regions implicated in top-down control (especially the right IPS) and lowering the threshold for distractors to gain access to task-relevant resources. This idea is consistent with my previous findings.

The possibility that we did not capture all active brain regions with the analyses cannot be ruled out. However, the fact that no significant clusters were observed in left-lateralized regions belonging to the default-mode network is interesting given such regions have been recently implicated in mental rotation and imagery (Cai et al., 2017). This could explain why, in the stress-induced study (chapter 3), individuals with an internal locus of control out-performed other individuals in mental rotation after introduction of the psychosocial stressor. As discussed (Chapter 3), “internals” are suggested to have superior top-down control than their external counterparts, especially on cognitive tasks requiring left-hemispheric support (Declerck, Boone, & De Brabander, 2006). If left-hemispheric regions of the default-mode network support attention to and manipulation of internal representations, it is likely that regions of the frontoparietal control network (FPCN), which are known to couple flexibly with other subsystems depending on task demands, mediate this activity. In theory, internals are better at

coordinating this FPCN, allowing them to block out task-irrelevant thoughts that would otherwise compete with and impair task-relevant internal processes, especially when they are left-hemispheric. Left-lateralized regions of the default mode network are engaged by anxious apprehension (as with the induction of a psychosocial stressor), and these same areas are implicated in mental rotation and imagery. It makes sense, then, that an increased ability to direct resources to goal-directed behaviour (an ability mediated by the FPCN) would facilitate the suppression of competing activity, preserving performance despite distraction. This ability would not be as advantageous, however, with tasks that rely on right-lateralized dorsal attention regions (like the delayed match-to sample task), which do not overlap with implicated regions of the default mode network.

In sum, the present results support the idea that visual working memory involves a complex interplay between distributed networks. Further study of the dynamic changes that occur throughout visual working memory can help to elucidate the interactions that mediate important aspects of task performance, aspects that are often overlooked. A more thorough discussion of this theoretical exchange, as well as a review of corroborating and antagonistic results obtained throughout my experiments follows in the final chapter of this dissertation.

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## Chapter 5: General Discussion

A network of frontal and parietal regions has been implicated in a wealth of cognitive functions ranging from imagery, episodic retrieval and general intelligence more broadly (Lückmann, Jacobs, & Sack, 2014). Researchers have suggested that working memory, a fundamental element in many higher order functions, is the underlying process supported by this core network. Although the importance of the fronto-parietal network in working memory is consensual amongst many researchers, the one-to-one mapping of brain loci to working memory functions has been problematic (e.g., Logie & D'Esposito, 2007), and recent research suggests working memory may not be restricted to these areas alone (Lamp, Alexander, Laycock, Crewther, & Crewther, 2016). Indeed, a large portion of the research associating these regions with visual working memory comes from maintenance-centric tasks, despite Baddeley's explicit inclusion of a manipulation component in his original model. Because of this, it is not clear that the same frontoparietal network typically implicated in a broader conceptualization of working memory underlies both the maintenance and manipulation of visual information. While some researchers contend that the same pattern of brain activity that sustains the temporary storage of information is sufficient for mental imagery of the kind involved in mental rotation (Cattaneo, Vecchi, Pascual-Leone, & Silvanto, 2009; Lückmann et al., 2014), other research implicates regions beyond this frontoparietal network.

More recently, research has questioned the utility of partitioning the brain into regions that perform specific, discrete functions. Instead, systems neuroscience is adopting the view that cognition arises out of the flexible and dynamic interaction of

large-scale networks. In line with this, this thesis is centred on the idea that *several* large-scale networks, which are broadly divided into extrinsic and intrinsic systems interact flexibly with each other to participate in a range of cognitive processes. While a relatively invariant core of brain regions may indeed be found to support a myriad of working memory tasks, this thesis explored the recruitment of additional extrinsic/intrinsic network components depending on task demands. To review, within the extrinsic system, the dorsal attention network mediates top-down control of sensory networks, (Corbetta & Shulman, 2002; Zabelina & Andrews-Hanna, 2016) and consists of the frontal eye fields and the dorsal parietal cortex (particularly the intraparietal sulcus (IPS) and superior parietal lobule) (Corbetta, Patel, & Shulman, 2008; Fox et al., 2005). The ventral attention network is involved in reorienting, and overlaps with regions involved in salience detection including the temporoparietal junction (TPJ) and ventral frontal cortex. Within the intrinsic system, the core regions of the default mode network include the medial prefrontal cortex and posterior cingulate cortex (Buckner, Andrews-Hanna, & Schacter, 2008; Spreng, Sepulcre, Turner, Stevens, & Schacter, 2013). The fronto-parietal control network is divided into the central executive and cingulo-opercular subsystems, with the central executive network anchored in the dorsolateral prefrontal cortex (Postle, 2006).

Research suggests that while control regions couple with extrinsic networks in order to direct attention to the external environment, they merge with intrinsic networks when attention is directed inward. These network reconfigurations occur across a range of cognitive tasks, such as visual search and spatial processing on the external side, and during memory and prospective planning on the internal end. In addition to successful

task completion, it appears that many cognitive states, including those associated with certain psychopathologies (Menon, 2011), are also associated with dynamic changes in these networks (Burdwood et al., 2016; Meehan, 2016; Spreng, 2012; Vossel, Geng, & Fink, 2014). In particular, two subtypes of stress – anxious arousal and anxious apprehension – provoke increased activity in different extrinsic/intrinsic network subregions. In the case of anxious arousal, activation increases in the ventral attention network (Abboud et al., 2006; Corbetta & Shulman, 2002; Critchley, 2009; Etkin & Wager, 2007; Fisher et al., 2014; Menon, 2011; Meyer, Strittmatter, Fischer, Georg, & Schmitz, 2004) and functional connectivity is disrupted within the dorsal attention network (Greene & Soto, 2014; McMenamin, Langeslag, Sirbu, Padmala, & Pessoa, 2014; Sridharan, Levitin, & Menon, 2008). Anxious apprehension, on the other hand, shifts activity to regions of the default mode network, which show increased coupling with regions of the central executive network (Bijsterbosch, Smith, Forster, John, & Bishop, 2014; Rossi & Pourtois, 2014). These differential activity patterns associated with cognitive state changes can lead to systematic and predictable cognitive impairments, such as those reported in subclinical populations (Menon, 2011; Young et al., 2016). This dichotomy presents an opportunity to investigate constraints imposed by such cognitive state changes on cognitive features of interest, and exploits the principle of cognitive economy - the fact that particular brain regions participate in more than one cognitive function. When network regions are already engaged in an ongoing state or function, they are less available to support additional tasks they might otherwise facilitate.

In this thesis, a quantitative meta-analysis was conducted (Chapter 2) that used stress as a paradigm to investigate the differential effects of endogenous and exogenous distraction on visual working memory task performance. This meta-analysis confirmed research suggesting different dynamics between arousal and apprehension, and the idea that these dynamics can lead to predictable influences on cognition. In essence, this meta-analysis supports the idea that anxious arousal increases activity in the ventral attention network, interrupts dorsal attention network activity and impairs right lateralized top-down attention to external stimuli. It also supports the idea that anxious apprehension can hijack the default mode network and impair top-down attention to internal representations. This meta-analysis also served as a preliminary confirmation that the visual tasks employed in visual working memory research may vary in terms of extrinsic/intrinsic network support, and that understanding these differences can help to predict cognitive constraints provoked under various circumstances. In order to investigate this idea further, the meta-analysis was followed by two controlled studies that further explored the differential effects of independent contextual constraints on maintenance and manipulation - a controlled stress study (Chapter 3) designed to increase apprehension and interfere with top-down control to internal stimuli, and an electroencephalographic (EEG) study (Chapter 4), where participants were required to store visual information in the face of an ongoing external distractor. Taken together, the data presented from these three studies suggest that key differences between the maintenance and manipulation may reflect the variable interplay between extrinsic and intrinsic networks.

With respect to maintenance, the present results implicate right-lateralized extrinsic network regions. In particular, source localization techniques employed in the EEG study (Chapter 4), indicated maintenance related activity increases in the right frontal eye fields and intraparietal sulcus. As predicted, results were also indicative of load-related decreases in right-lateralized ventral attention regions (i.e., the right temporoparietal junction), consistent with earlier suggestions that ventral attention network suppression is important for successful task completion on tasks requiring top-down control of attention to external stimuli (as well as to their internal representations). It is also consistent with the idea that an increase in right-lateralized ventral attention network activity, brought on by cognitive state changes, can alter dynamics that otherwise support maintenance tasks. Such alteration can lead to impaired performance of the kind found in the meta-analysis presented in Chapter 2, where arousal-induced ventral attention network activity impaired performance on visual tasks predicted to rely on right dorsal attention regions. This finding is also consistent with the idea that effects induced by bottom-up ventral attention are faster and more transient than those induced by top-down dorsal attention (Tang, Wu, & Shen, 2016). As recruitment of right lateralized dorsal attention regions increased with increased working memory load, irrelevant external distractors were less likely to activate ventral attention regions that would otherwise compete with task performance.

Increased maintenance loads were associated with increased activity in the right dorsolateral prefrontal cortex (dlPFC) in a subset of individuals (Chapter 4). While the right dlPFC has been implicated in a resounding number of visual working memory experiments, its suggested role has been contentious. Originally, it was presented as the

neural substrate for working memory, a suggestion that was based on its observed continued activity during the delay period of working memory tasks in primates (Baddeley, 2003; Goldman-Rakic, 1987). However, more recent research has questioned this view (Lara & Wallis, 2015; Rieckmann, Pudas, & Nyberg, 2017). Instead, research suggests that activation of parietal working memory areas along with the visual cortex is sufficient for tasks that require the maintenance of perceptual information from the environment (Rieckmann et al., 2017). Rather than a locus of storage, prefrontal cortex involvement is suggested to relate to active focus on relevant sensory representations, the downregulation of irrelevant representations (Gómez-Ariza, Martín, & Morales, 2017) and executive function (Postle, 2006). Consistent with other research noting between group and intra-individual differences in right dlPFC recruitment, (e.g., Gómez-Ariza et al., 2017), activity in this region was observed in only a subset of participants in the EEG study (Chapter 4). Reasons for this selective activity are unclear, but could reflect an innate predisposition, or a compensatory mechanism (e.g., reflective of increased strategy use in individuals with low imaging ability, or as a method of suppressing task-irrelevant thoughts in certain participants). The present results also suggest maintenance related activity modulation in the right medial prefrontal cortex (Chapter 4), a region of the default mode subsystem of the intrinsic network. While results are slightly difficult to fully parse, various source modeling attempts have also localized working memory induced increases in frontal theta to the medial prefrontal and anterior cingulate cortex (Onton, Delorme, & Makeig, 2005; Scheeringa et al., 2009). Simultaneous EEG-fMRI experiments have documented a negative correlation between load-induced increases in EEG theta and blood oxygen level dependent (BOLD) activity in these regions, taking

this to reflect a working memory-related suppression of default mode network activity (Scheeringa et al., 2009), which is consistent with my findings. To summarize, in addition to a core network of frontoparietal regions often implicated in visual working memory, converging evidence from this thesis suggests further recruitment of right-lateralized regions of the extrinsic network.

While the default mode network has typically been interpreted as an index of task negative activity, recent research has emphasized its heterogeneous nature, highlighting its variable involvement according to task demands. In line with this, results presented in this thesis (Chapter 2, Chapter 3) suggest default mode regions may participate in mental rotation activity. In particular, the meta-analysis (Chapter 2) supports the idea that tasks requiring more attention to imagery based internal mental representations are impaired when regions of the default mode network couple with control regions that shift attention toward unconstrained, internally-directed thought (Qin, Hermans, van Marle, Luo, & Fernández, 2009). A mediation effect was found in the stress experiment (Chapter 3) indicating that individuals with an internal locus of control out-performed individuals with less feelings of control on a mental rotation task only. While speculative, these results point to involvement of left-hemispheric support on the mental rotation task. This interpretation is based on an “activation-arousal” model which posits that individuals with an internal locus of control rely on a left-lateralized dopaminergic activation system for self-regulation, which affords these individuals superior sustained internal attention, especially on left-hemispheric tasks.

Beyond these findings, the electroencephalographic (EEG) study (Chapter 4) did not implicate any maintenance related activity in left-lateralized regions belonging to the

default-mode network. This could explain why, in the stress study (chapter 3), individuals with an internal locus of control out-performed other individuals in mental rotation after stress induction. As discussed (Chapter 3), “internals” are suggested to have superior top-down control relative to their external counterparts, especially on cognitive tasks requiring left-hemispheric support (Declerck, Boone, & De Brabander, 2006). If left-hemispheric regions of the default-mode network support attention to and manipulation of internal representations, it is likely that regions of the frontoparietal control network (FPCN), which are known to couple flexibly with other subsystems depending on task demands, mediate this activity. In theory, internals are better at coordinating this FPCN, allowing them to block out task-irrelevant thoughts that would otherwise compete with and impair task-relevant internal processes, especially when they are left-hemispheric. Left-lateralized regions of the default mode network are engaged by anxious apprehension (as with the induction of a psychosocial stressor), and these same areas are implicated in mental rotation and imagery. It makes sense, then, that an increased ability to direct resources to goal-directed behaviour (an ability mediated by the FPCN) would facilitate the suppression of competing activity, preserving performance despite distraction. This ability would not be as advantageous, however, with tasks that rely on right-lateralized dorsal attention regions (like the delayed match-to sample task), which do not overlap with implicated regions of the default mode network.

Some research has shown an overlap in a core fronto-parietal network for visual maintenance and imagery of the kind employed in mental rotation (Cattaneo et al., 2009; Lückmann et al., 2014). However, results from this work suggest recruitment of default mode regions beyond this core network. This is consistent with other research that

documents: further neural recruitment of functionally relevant areas beyond a core network of working memory components for manipulation (Lamp et al., 2016); the coupling of the default mode and frontoparietal control networks in the service of internal goal-directed behavior (e.g., autobiographical planning (Spreng, Stevens, Chamberlain, Gilmore, & Schacter, 2010)); central executive and default mode network involvement in mental rotation (Cai et al., 2017; Gao et al., 2017); an involvement of left-lateralized default mode regions in imagery-related processes (Boucard et al., 2016; Cai et al., 2017; Zimmer, 2008).

### **Conclusion**

The present results provide converging evidence supporting the idea that visual working memory involves a complex interplay between distributed large-scale networks. In recent years, systems neuroscience approaches have emphasized a network-centered approach to understanding brain function. Attempts to elucidate a visual working memory network have implicated frontoparietal regions. However, these attempts have taken a maintenance-centric approach and have, for the most part, neglected to systematically consider whether findings apply to tasks that call for manipulation of visual information in addition to its maintenance. Many of these attempts have also neglected to implement complimentary methodologies in order to provide converging evidence that points to specific large-scale network contributions to visual maintenance and manipulation. Such converging evidence is vital in cognitive science – a science that uses empirical data to infer causal sources – because there is more than one potential solution to such inverse problems. Thus, while the significance of some of the findings in this thesis are speculative, the fact that different paradigms led to converging

conclusions is promising. The studies presented in this thesis support and further extend the view of a dynamic interaction between several large-scale networks in support of visual working memory. These results suggest that, rather than an invariant core network of regions that supports visual working memory, different tasks engage additional regions depending on specific demands. Understanding the nuances of this dynamic interplay is important, given the nature of cognitive economics in that brain regions participate in a range of cognitive functions. With a better understanding of how large-scale networks might differentially contribute to cognitive functions, as well as how changing network dynamics engender cognitive state changes, research can better predict what kinds of cognitive constraints are likely to occur with contextual changes. A consideration of the dynamic and flexible nature of these large-scale networks is an imperative step for future theoretical models of visual working memory.

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