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Functional Connectivity of Thalamocortical Networks in Visual Working Memory

A Dissertation Presented

by

Anna Song Huang

to

The Graduate School

in Partial Fulfillment of the

Requirements

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The Graduate School

Anna Song Huang

We, the dissertation committee for the above candidate for the
Doctor of Philosophy degree, hereby recommend
acceptance of this dissertation.

Dr. Hoi-Chung Leung
Associate Professor of Department of Psychology

Dr. Brenda Anderson
Associate Professor of Department of Psychology

Dr. Aprajita Mohanty
Assistant Professor of Department of Psychology

Dr. Chiang-Shan (Ray) Li
Associate Professor of Psychiatry and of Neuroscience at Yale School of Medicine

This dissertation is accepted by the Graduate School

Charles Taber
Dean of the Graduate School

Abstract of the Dissertation

Functional Connectivity of Thalamocortical Networks in Visual Working Memory

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Anna Song Huang

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Visual working memory refers to the temporary maintenance and manipulation of information to achieve a goal and is thought to involve a network of frontal, parietal and visual regions. Accumulating evidence suggests that the thalamus is also involved in visual attention and working memory. The thalamus shows extensive neuroanatomical connectivity with cortical regions involved in working memory and is hypothesized to play an important role in the synchronization of task dependent activity among cortical networks. However, work on functional connectivity between the thalamus and cortex during visual and visuo-spatial working memory in humans is sparse. The studies reported here applied functional magnetic resonance imaging in humans to investigate (1) functional connectivity between thalamus and cortical regions involved in visual working memory and (2) the association between thalamocortical connectivity with neural representation of memorized visual stimuli, and with behavioral performance. Study 1 investigated thalamocortical connectivity during selective maintenance of face and scene stimuli. We showed that thalamocortical connectivity varies in accordance with the relevance of the to-be-remembered visual category; connectivity between the thalamus and category selective visual regions are greater when a region's preferred stimulus category is relevant, compared to when it is irrelevant to task goals. Further, stronger functional connectivity between the thalamus and the fusiform face area (FFA) was associated with greater behavioral advantage of selectively maintaining face stimuli over maintaining both face and scene stimuli. Study 2 investigated whether variation in thalamocortical connectivity while maintaining visual stimuli is associated with subsequent visual search performance. We showed that different search performance measures are differentially associated with thalamocortical and cortico-cortical connectivity. We found no clear relationship between thalamocortical connectivity and representation in visual working memory. Together, these findings suggest that, along with the better studied cortico-cortical connectivity, thalamocortical connectivity is an important component of the visual working memory system and is associated with behavior.

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List of Abbreviations

BOLD: blood-oxygenation-level-dependent

FEF: frontal eye fields

FFA: fusiform face area

IPL: inferior parietal lobule

IPS: intraparietal sulcus

LFP: local field potential

LOC: lateral occipital complex

MD: mediodorsal nucleus

MFG: middle frontal gyrus

MVPA: multivoxel pattern analysis

PFC: prefrontal cortex

PPA: parahippocampal place area

PPC: posterior parietal cortex

PPI: psychophysiological interactions

pre-SMA: pre-supplementary motor area

RDM: representational dissimilarity matrix

RSA: representational similarity analysis

SPL: superior parietal lobule

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Chapter 1

General Introduction

Working memory refers to the temporary maintenance and manipulation of information to achieve a goal and is central to many cognitive tasks. Working memory deficits have been shown in multiple psychiatric and neurological disorders [1–3], highlighting the importance of research into the neural processes underlying working memory. Traditionally, research into the neural substrates of visual working memory have focused on cortical regions including prefrontal, parietal, visual and visual association regions [4–12] (see refs. [13–16] for review) with the dominant theory proposing that the prefrontal cortex provides top-down control of visual representations maintained in visual and visual association regions [17].

The thalamus has been increasingly recognized as having a vital role in cognition [18–21] and is thought to be involved in influencing cognition through its functional connectivity with cortical regions [22,23]. One prominent theory proposes that the thalamus drives synchronization between cortical areas to enhance goal directed behaviors [20,24,25]. This theory is supported by the finding that disruption of thalamic activity leads to a disruption of goal dependent cortico-cortical connectivity [24,26]. It is further supported by neuroanatomical evidence showing that there are parallel anatomical cortico-cortical and cortico-thalamocortical connections in the brain [23]. The thalamus is extensively interconnected with cortical regions involved in working memory, as well as being the main output structure for the basal ganglia (see refs. [27–30] for reviews), a region implicated in information gating for working memory [31,32]. Our understanding of the role the thalamus plays in working memory and attention in humans is limited. It is possible that the thalamus has a role in mediating cortico-cortical connectivity between the prefrontal, parietal and visual association regions during working memory and attention.

The goal of this thesis was to examine behavioral modulation of thalamocortical and cortico-cortical connectivity during visual working memory and attention in humans. We tested the hypothesis that the thalamus has a mediating role in cortico-cortical connectivity, and that thalamocortical connectivity is

modulated by behavior. Based on findings in non-human primates showing that the thalamus is necessary for target related enhancement of neuronal activity in visual regions [20,26], we further tested whether increased thalamocortical connectivity is associated with better visual representations and working memory performance.

Aim 1 of this thesis was to examine the association between behavior, thalamocortical and cortico-cortical connectivity. *Study 1* investigated this by comparing thalamus and prefrontal connectivity with visual association regions while varying the task relevance of each visual region's preferred stimulus category (fusiform face area [FFA] for face stimuli, parahippocampal place area [PPA] for scene stimuli). We further investigated the unique association of thalamocortical and cortico-cortical connectivity with task relevance using path analysis to model the mediating effect of thalamic activation on cortico-cortical connectivity while varying the task relevance of face and scene stimuli. *Study 2* more explicitly examined how behavior interacted with the mediation effect of thalamic activation on cortico-cortical connectivity using path analysis models on trial-by-trial measures of blood-oxygenation-level dependent (BOLD) signals and behavior. Search efficiency is thought to improve with better target representations, and we examined two separate parts of a commonly used measure of search efficiency (reaction time) to compare how the attention component of visual search and the target recognition component differentially modulate cortico-thalamo-cortical connectivity and cortico-cortical connectivity during the delay and at search.

Aim 2 of this thesis examined the association between thalamocortical connectivity and visual representation of items in memory. *Study 1* explicitly tested the association between thalamocortical connectivity and categorical representation of Faces and Scenes in the FFA and PPA using representational similarity analysis (RSA). *Study 2* indirectly examined representation by using behavior as a proxy for target representation. To better isolate target representation in a visual search task, we measured the modulatory effect of different search performance measures on thalamocortical and cortico-cortical connectivity during the delay period when search targets are held in memory in preparation for search.

Chapter 2

Background and Significance

Cortical Networks of Working Memory

An extensive body of literature has investigated the cortical regions involved in visual and visuospatial working memory maintenance and manipulation. Early electrophysiological work in nonhuman primates found that neurons in the dorsolateral prefrontal cortex (PFC) [9–12], posterior parietal cortex (PPC) [8,33,34] and inferior temporal cortex (IT) [35] show stimulus specific sustained neural activity during the delay period of visual and visuospatial working memory tasks. Neuroimaging literature complemented the electrophysiology studies, finding that regions in the prefrontal and parietal cortices showed sustained BOLD activation during the delay period of visual and visuospatial working memory tasks [4–7], as well as showing greater activation for accurate compared to error trials [36,37]. More recent neuroimaging studies have used multivoxel pattern analysis (MVPA) to investigate information maintained in the spatial activation patterns of frontal, parietal and visual regions during the delay period of visual and visuospatial working memory tasks [38–45]. Such studies have found that stimulus features (such as orientation) [39,41–45] as well as stimulus categories (such as faces or scenes) [38,40] can be classified during the delay period even in the absence of sustained activation, and that fidelity of decoding is associated with the precision of memorized stimuli [44]. Stimulus feature information can also be decoded from frontoparietal regions, which do show sustained activation throughout the delay period of working memory tasks [46,47].

Functional connectivity between frontoparietal and visual association regions have also been shown to vary with task demands. The prefrontal cortex and visual association regions are functionally connected during the delay period of visual working memory tasks [48]. This connectivity is greater when cued to remember preferred stimulus categories rather than ignore them [49,50] and shows parametric increases with memory load [51]. Primate electrophysiology studies have shown that disruption of the dorsolateral prefrontal cortex attenuates stimulus specific persistent activity in visual association cortices during working memory

maintenance [52], and a human transcranial magnetic stimulation (TMS) found that disruption of the inferior frontal gyrus (IFG) reduces stimulus selectivity for faces and scenes in visual association regions, with the degree of reduction coinciding with decreases in performance [53,54]. A putative mechanism for how cortical regions interact during working memory is through synchronization of oscillations across disparate cortical regions [55,56].

Most theories of working memory focus on cortico-cortical interactions. However, many anatomical cortico-cortical connections have parallel cortico-thalamo-cortical connections [23], indicating that the thalamus may mediate cortical communication [57]. The prefrontal cortex also sends projections to the basal ganglia, which in turn projects through the thalamus back to the prefrontal cortex and this cortico-striatal-thalamic loop is believed to be important for information gating in working memory [27,29]. This anatomical connectivity pattern suggests that the thalamus is important to working memory and may interact with cortical regions and the basal ganglia during working memory.

Thalamocortical Networks

The neuroanatomical connectivity of the pulvinar and mediodorsal (MD) thalamus suggest that these two higher order nuclei are likely involved in visual working memory and attention (see Figure 2.1). Anatomical tracing studies find that the MD shows extensive reciprocal connections with the prefrontal cortex [58–60], with the parvocellular subdivision (MDpc) showing most connectivity with the dorsolateral PFC [59]. In comparison, the pulvinar shows extensive reciprocal connections with both the PPC and occipitotemporal cortex [61–66].

Despite both the dorsolateral PFC and PPC showing connections to the medial pulvinar and MDpc, a study using double anterograde labelling showed that neurons from the PFC and PPC terminate on separable populations of neurons [60]. Similarly, while both the occipitotemporal cortex and PPC show anatomical

connections with the medial, lateral and dorsolateral subdivisions of the pulvinar, neurons from the PPC and occipitotemporal cortex terminate on separable populations of neurons in the pulvinar [63].

In humans, it is difficult to identify the pulvinar and mediodorsal thalamus without high resolution imaging. However, researchers have shown that by using structural and resting-state functional connectivity seeded in cortical regions, it is possible to parcellate the thalamus in a way that is qualitatively similar to post mortem identification of thalamic nuclei in humans [67–71]. It is also possible to parcellate the thalamus based on independent component analysis of dissociable signals in the thalamus [72]. The most promising evidence for the efficacy of this work is from the finding that connectivity from the subdivisions of the MD to different subdivisions of the PFC shows consistency with findings from tractography of anatomical connectivity in monkeys [69].

Thalamus in Cognition

A recent theory of thalamic involvement in cognition proposes that higher order thalamic nuclei (including the MD and pulvinar) mediates neuronal synchrony between different networks of cortical neurons in a behaviorally relevant manner [20,73]. Under this framework, higher order thalamic nuclei might increase synchrony between cortical neurons of one network while not in another network in accordance with behavioral relevance, with the synchrony increasing efficacy of information transfer [73].

The finding that synchronization of neural activity between the pulvinar and cortical regions varying with behavioral goal provide evidence for this synchronization theory of thalamic function [20,26]. Saalman and colleagues [20] found that in a task where monkeys were trained to discriminate a spatially cued stimulus, pulvinar-V4 and pulvinar-TEO synchrony increased depending on cue location. They used Conditional Granger Causality Analysis (GCA) to examine the influence of the pulvinar on V4 and TEO in the frequency domain. Their results suggest that the pulvinar influenced oscillatory activity in the V4 and TEO when attending to a location within the receptive field (RF), but that V4 oscillatory activity did

not influence TEO when controlling for pulvinar. In a similar study, Zhou and colleagues [26] examined the effect of a spatial cue on stimulus specific neuronal activity in, and synchronization between, the pulvinar, V4 and IT. They found that when preferred stimuli were targets (attended), neurons in the V4 and pulvinar both showed increased firing rates. They also found coherence between V4 spikes with local field potentials (LFP) in the V4, IT and pulvinar increased with attention. Attention dependent coherence increases were also seen between pulvinar spikes and V4 LFP, but not with local pulvinar LFP. They used GCA to examine timing of attention effects on V4 and pulvinar LFP and found that gamma frequency changes in V4 LFP preceded pulvinar LFP changes. However, reversible deactivation of the pulvinar severely reduced the attention effects in both V4 and IT firing rate, and coherence between V4 and IT. It has been shown previously that reversible lesions to the pulvinar can reduce cortical excitability in the V1, particularly for preferred orientations [74]. It is possible that the pulvinar may influence cortical excitability generally, and that the effect is more apparent when attention is required.

In human neuroimaging literature, the pulvinar shows greater activation during attention shifts and distractor suppression [75,76], as well as the ability to classify above chance attended features and locations from the pulvinar [77]. While there is little evidence to suggest that the pulvinar is involved in active maintenance of information within working memory, the processes of selective attention and selective maintenance show similar properties and the cortical regions involved in attention and working memory overlap [78,79]. Indeed, items in working memory may bias attention processes even when irrelevant to the attention task, and this biasing is associated with increased pulvinar activation [80,81]. In a study using meta-analytic connectivity modelling (MACM), the pulvinar showed consistent coactivation with cortical regions involved in action, cognition, motion and perception, suggesting that it has widespread patterns of connectivity that spans multiple behavioral domains, though its coactivation with occipital visual areas only occurred when examining studies in the ‘cognitive’ domain [82].

Lesions in the primate pulvinar have been shown to produce impairments in visual search, cued spatial orienting, and the selection of spatially guided actions [83–85], though another study indicates that pulvinar

lesions do not lead to a deficit in visual search [86]. In humans, pulvinar and posterior thalamus lesions are associated with spatial neglect [87,88], deficits in discriminating target features in the presence of salient distractors [89] and cue related enhancement in selective attention [81]. Electrophysiology, neuroimaging and lesion studies all indicate that the pulvinar is involved in selective attention for spatial location and visual stimuli.

The MD has long been associated with working memory processes [12,90]. Different populations of MD neurons show stimulus specific responses during the cue, delay and response periods of an oculomotor response task [91–93]. There is also some evidence to suggest that the MD has a role in increasing synchrony between networks of cortical neurons [24]. In a study examining spatial working memory in mice (T-maze delayed non match-to-sample task), beta frequency synchrony between MD and PFC increased during the acquisition period of the task, while disruption of the MD decreased this phase lock, as well as reducing performance in the task [24]. Deactivation of the prefrontal cortex also disrupts MD neuronal firing in a spatial working memory task in primates [90].

Human neuroimaging literature is sparse in specifically examining the role of MD in working memory and attention, though thalamic activation in working memory tasks when memory conditions are compared to a no-memory baseline is frequently seen. This activation shows little distinction between type of working memory (visual, visuospatial, or verbal) [94,95], and is common to both working memory and attention [96]. Thalamus has also shown increased activation associated with the encoding of correct trials [36] and increased connectivity with visual regions during the delay period of a working memory task [48].

Lesion data further indicate that the MD is a necessary part of the network underlying working memory. In humans, thalamic infarctions that include the MD (often, but not always in conjunction with the anterior nuclei) results in executive function deficits, measured as set-shifting and response inhibition, but not short term memory as measured by memory span [97]. Primate studies with more circumscribed lesions in the MD result in impairments in a spatial response task [98], a visual delayed non match-to-sample task [99]

and trial unique, but not stimulus repeating match-to-sample tasks [100]. Therefore, the MD should be a focus of study into thalamic involvement in working memory.

Electrophysiology, lesion and neuroimaging studies all indicate that the thalamus has a role in attention and working memory, and investigations in non-human animals suggest that the thalamus might have a role in attention mediated synchronization of neuronal activity between and within cortical regions. However, there are not many studies investigating how thalamocortical connectivity in humans supports working memory and attention. Here we sought to examine if there is evidence to support that the thalamus shows differential functional connectivity with cortical regions during the maintenance phase of working memory in humans as a function of task goals and behavioral outcomes.

Chapter 3

Study 1: Thalamocortical connectivity associated with selective maintenance of Face and Scene stimuli

Background and Rationale

Selective maintenance refers to the ability to maintain stimuli relevant for task goals in working memory while ignoring irrelevant stimuli [101]. A network of prefrontal, parietal and visual association regions are thought to be involved in selective maintenance [38,50,101–103]. A prominent theory posits that the prefrontal cortex sends biasing signals to visual association cortices in accordance with task goals [104]. In this study, we examined task dependent differential thalamocortical and cortico-cortical connectivity.

Since the discovery of stimulus specific sustained neuronal activity in the prefrontal cortex [12], the focus of research into the neural basis of visual and visuospatial working memory has been on cortical regions. This extensive body of work has identified a network of cortical regions consistently involved in working memory processes, including, but not restricted to the lateral prefrontal cortex (PFC), the precentral sulcus/frontal eye fields (FEF), pre-supplementary motor area (pre-SMA), posterior parietal cortex (PPC) regions, including the intraparietal sulcus (IPS), inferior and superior parietal lobule (IPL and SPL) [4–7], and more recently visual and visual association regions in the occipitotemporal cortex [38–40,45] (see refs. [17] for review). Studies of visual working memory show differential functional connectivity between the prefrontal cortex and visual association regions as a function of task demand [102], and functional connectivity to visual association regions that preferentially process specific stimulus categories (faces or scenes) increases with stimulus relevance [48,50,103] and stimulus load [51]. Perturbations to the lateral inferior frontal region using transcranial magnetic stimulation (TMS) has been shown to disrupt functional connectivity between the right inferior frontal gyrus (IFG) and right fusiform face area (FFA) during visual working memory [53,54]. Baseline connectivity (measured during the sham TMS) predicted change in

accuracy after TMS application to the IFG. TMS to the IFG led to reduced selectivity for face stimuli in the occipitotemporal cortex, which was also associated with decreased performance [53]. While these studies support the theory that the prefrontal cortex biases activation in visual association regions in a task dependent manner, how this occurs remains unknown. One hypothesis posits that long range synchronization of oscillatory activity between cortical regions plays a role in this process [55,56]. This oscillatory signal has been observed in the theta and alpha ranges, and the thalamus is thought to drive alpha frequency synchronization within and between visual regions [20,26].

It is possible that the thalamus plays a role in increasing synchrony between the prefrontal cortex and visual association regions during working memory maintenance. The thalamus is known to share extensive reciprocal connections with the prefrontal cortex [58,59], and it has been shown that synchronization between local field potentials (LFP) in the mediodorsal thalamus (MD) and PFC increase during spatial working memory tasks in mice [24]. Thalamic deactivation has been shown to disrupt neuronal activity in the PFC [24], and PFC deactivation disrupts thalamic activity in the MD [90]. Neuronal activity in the MD share similar activity profiles to neurons in the dorsolateral PFC during the cue, delay and response period of oculomotor delayed response tasks [91–93]. Along with the MD, pulvinar neurons respond similarly to neurons in the parietal cortex during the presentation of visual stimuli and for spatial selective attention [83]. Deactivation of the pulvinar has been shown to disrupt activity in the V4 as well as V4 coherence with the inferior temporal cortex during a change detection task with a spatial cue indicating location to attend [26]. The pulvinar has been investigated as a model of how higher order thalamic nuclei may influence cognition [20,73]. This theory proposes that the thalamus selectively increases synchrony between networks of cortical neurons as a function of behavioral relevance. Many anatomical cortico-cortical connections show parallel cortico-thalamo-cortical connections [23] though there is little evidence for connections between thalamic nuclei, except through the reticular nucleus [105]. This pattern of neuroanatomical connectivity has led to theories proposing that the thalamus has a role in mediating neural activity between cortical regions [23], possibly by influencing synchronization between cortical regions.

In recent years, neuroimaging studies have begun to examine how thalamocortical connectivity may be used to parcellate the thalamus, though studies finding thalamic involvement in visual working memory have focused on the thalamus as a whole. The thalamus as a whole is involved in tasks with increased cognitive demand for both visual attention and working memory [96]. Further, connectivity analyses seeded from the fusiform face area (FFA) shows connectivity with the thalamus during a visual working memory task for face stimuli (see Fig. 4 in [48]). While investigating the thalamus as a whole may provide information about the role of the thalamus in visual working memory, there has been a great interest in parcellating the thalamus into its component regions based on structural connectivity with diffusion tensor imaging (DTI) and functional imaging at rest. These studies showed that the thalamus can be parcellated based on its structural and functional connectivity patterns with different cerebral subdivisions [67–69,71,106] and cortical networks [70]. Independent component analysis (ICA) has also been used to parcellate the thalamus by dissociating signals across voxels based on their time courses [72]. Parcellations derived from these methods show qualitative similarity with a parcellation of the human thalamus based on post mortem analysis [107]. By using the results of these parcellations, we can examine the role of thalamic regions that are structurally connected to our cortical regions of interest. Specifically, we investigated differential thalamocortical connectivity to different visual regions as a function of task demand during the delay period of a visual working memory task. *To investigate thalamocortical and cortico-cortical connectivity in response to differing task demands, we reanalyzed the data from studies previously reported in Le et al., (under review) and Oh & Leung (2010). To test the influence of task goals on thalamocortical connectivity, we varied the relevance of stimulus categories (faces or scenes) and measured connectivity between the thalamus and visual regions that prefer these stimulus categories (fusiform face area [FFA] and parahippocampal place area [PPA] respectively) when their preferred stimulus is relevant, compared to when it is irrelevant.*

Using the same data, we also investigated whether thalamocortical connectivity was related to visual representation of items in memory, as has been suggested by electrophysiological studies of thalamic

involvement in attention [26] and multivariate pattern classification analysis (MVPA) of contrast gratings in the pulvinar nucleus [77]. We chose to use Representational Similarity Analysis (RSA) as a proxy of representation [108]. RSA uses the second level correlation between a model of representational similarity and the neural similarity of different categories/stimuli to determine how close neural representation is with a hypothesized model of representation. There are few studies directly testing the association between RSA and behavior, though RSA is greater during a verbal 2-back task when subjects respond correctly compared to when they miss the target [109]. Another study found that pattern similarity, a measure closely related to RSA, in the hippocampus and lateral occipital cortex (LOC) predicted later temporal memory [110].

We hypothesized that (1) thalamocortical and cortico-cortical connectivity would vary with the task goal (remembering face or scene stimuli) and (2) that the task goal influences cortico-cortical connectivity through the thalamus. We further predict that thalamocortical connectivity would be (3) associated with neural representation of the relevant stimuli and (4) behavioral performance.

Methods

Data used in this report were from previous studies investigating selective maintenance in healthy young adults and in major depressive disorder. Only data from healthy participants were included in this study. Complete descriptions of experimental designs and scanning protocols for *Experiment 1* can be found in Oh & Leung (2010) and for *Experiment 2* in Le et al., (under review). Critical details are summarized below.

Participants

Thirty-three young adults participated in this study (18 females; 18-33 years of age, mean = 22.4 years) (12 from *Experiment 1* and 21 from *Experiment 2*). Participants were recruited through flyers posted around the Stony Brook University campus. All participants had normal or corrected to normal vision (contact lenses only) and had no history of substance abuse. Written consent was obtained from participants in accordance with the Institutional Review Boards at Stony Brook University and participants were compensated monetarily.

Behavioral Task

The working memory task consisted of a delayed match-to-sample task with a retroactive cue (see Figure 3.1A). Each trial started with a green fixation on a black background (3000 ms for *Experiment 1*; 4000 ms for *Experiment 2*). A warning fixation (200 ms for *Experiment 1*; 500 ms for *Experiment 2*) was presented prior to the first stimulus display. Two stimuli were presented sequentially, a trial unique face and a trial unique scene stimulus (800 ms each) with an inter-stimulus interval (ISI) of 200 ms. A post stimulus delay was presented for (2500 ms for *Experiment 1*; 2200 ms for *Experiment 2*), followed by a 1000 ms cue indicating which condition the trial belonged to, Remember Scene was indicated with a “Scene”, Remember Face was indicated with a “Face” and Remember Both was indicated with a “Both”. The cue indicated

which stimulus/i the participant was required to remember. The cue was 100% valid. A post cue delay (9500 ms for *Experiment 1*, 9000 ms for *Experiment 2*) was followed by a 1000 ms probe stimulus consisting of a matching or nonmatching stimulus in the same category as cued. Participants indicated whether the probe matched the stimulus with a button press. The inter trial interval (ITI) varied between 8 and 14 s with a mean of 11 s for *Experiment 1* and between 8 and 12 s with a mean of 10 s for *Experiment 2*. Each run consisted of 12 trials, 4 per condition. Participants in *Experiment 1* did 5 runs resulting in 20 trials per condition, and participants in *Experiment 2* did 6 runs, resulting in 24 trials per condition in. The order of task conditions was counterbalanced across runs and participants.

The localizer task was used to identify the parahippocampal place area (PPA) and the fusiform face area (FFA) in individual participants. The localizer task consisted of a blocked 1-back task (8 blocks in *Experiment 1*; 12 blocks in *Experiment 2*), alternating blocks of Face stimuli, Scene stimuli, and for *Experiment 2* only, Object stimuli. Each block consisted of 8 trials from one stimulus category, with the stimulus being present for 800 ms followed by a 1200 ms ISI. Each block was 16 seconds followed by a 16 second rest block. Task blocks were counterbalanced within the run. Participants were instructed to respond yes/no using their right index and middle finger.

Image acquisition

Experiment 1 Both the working memory and localizer tasks were acquired using a Philips 3-Tesla Achieva System (Cleveland, OH). High resolution anatomical images were acquired with a T1-weighted three dimensional turbo field echo sequence (TR = 9.9 ms, TE = 4.6 ms, flip angle 25°, matrix = 256×256, FOV = 256×93.8 mm, 176 slices. T1 weighted in-plane anatomical images of 24 axial-oblique slices, parallel to the anterior commissure-posterior commissure (AC-PC) were also collected (TR = 300 ms, TE = 5 ms, flip angle = 60°, Matrix = 256×256, FOV 220×220 mm, slices = 24, slice thickness = 5 mm with 0 mm gap). Functional MRI images were collected using single-shot T2* weighted echo planar imaging (EPI) sequence

collected in the same prescription as the in-plane images (TR = 1500 ms, TE = 30 ms, flip angle = 80°, matrix = 64×64, FOV = 220×220 mm, slices = 24, slice thickness = 5 mm with 0 mm gap). The working memory task consisted of 240 volumes per run, with a total of 5 runs, with each run was preceded by 4 additional dummy volumes to allow the MR signal to reach equilibrium, these scans were discarded prior to analysis. For the localizer task, the same functional scanning parameters were used, except that the TR was 2 sec. The localizer task consisted of 136 volumes with 3 additional dummy volumes.

Experiment 2 Both the working memory and localizer tasks were acquired using a Siemens Trio 3 T System (Siemens, German). High resolution anatomical images were acquired with a T1-weighted gradient echo pulse (MPRAGE) sequence (TR = 1900 ms, TE = 2.53 ms, flip angle 9°, matrix = 256×256, FOV = 250×250 mm, 176 slices, slice thickness - 1 mm). T1 weighted in-plane anatomical images of 33 axial-oblique slices, parallel to the anterior commissure-posterior commissure (AC-PC) were also collected (TR = 300 ms, TE = 5 ms, flip angle = 60°, Matrix = 256×256, FOV 220×220 mm, slices = 33, slice thickness = 3.5 mm with 0.5 mm gap). Functional MRI images were collected using single-shot T2* weighted echo planar imaging (EPI) sequence collected in the same prescription as the in-plane images (TR = 2000 ms, TE = 30 ms, flip angle = 80°, matrix = 72×72, FOV = 220×220 mm, slices = 33, slice thickness = 3.5 mm with 0.5 mm gap). The working memory task consisted of 180 volumes per run, with a total of 6 runs, while the localizer task consisted of 200 volumes. Each run was preceded by 3 additional dummy volumes to allow the MR signal to reach equilibrium, these scans were discarded prior to analysis.

Preprocessing

All images were preprocessed in SPM8 (Wellcome Trust Center for Neuroimaging, University College London, <http://www.fil.ion.ucl.ac.uk/spm/>). The first 3 volumes of each functional run were discarded to allow T2* signal to reach equilibrium. The remaining functional images were corrected for differences in slice acquisition timing and head motion. A mean EPI image was then generated from the realigned images.

T1 weighted inplane structural image was co-registered with the mean EPI image, then the MPRage image was coregistered to the T1 weighted in-plane structural image. Segmentation was applied to the high resolution T1 structural image and segmented images were normalized to the Montreal Neurological Institute (MNI) template. The transformation parameters were then applied to all functional images. Finally, all functional images were smoothed with a Gaussian kernel of 4 mm at full-width-half-maximum (FWHM) and were high-pass filtered with a cutoff of 1/128 Hz.

First level model definition

A general linear model (GLM) was constructed for each participant with 4 events per condition (Stimulus, Cue, mid-Delay and Probe). The onset for each event was convolved to a hemodynamic response function (HRF). The mid-Delay was modeled as an impulse function at 4750 ms (*Experiment 1*) and 4500 ms (*Experiment 2*) after the Cue offset. Motion outliers were modeled as effects of no interest and removed through linear regression. Outliers were defined as volumes with frame-to-frame displacement of >0.05 mm translation or >0.02 radians rotation with the Artifact Detection Tools (ART, https://www.nitrc.org/projects/artifact_detect/). Outlier volumes ranged from 0-12% volumes of each run across all participants (mean 2%, sd 2%). To identify Scene selective activity during the delay period, we looked at the Remember Scene > Remember Face contrast for the mid-Delay event. To examine Face selective activity, we examined the Remember Face > Remember Scene contrast. To examine effects of load, we used the Remember Both > Remember Face+Remember Scene contrast, henceforth described as the Non Select > Select contrast. The results for *Experiment 1* and *2* were similar, all following analyses (PPI, path analysis and RSA) used individually defined ROIs and results from *Experiment 1* and *2* were combined.

ROI selection

The localizer task was used to identify the right FFA and right PPA in individual subjects. The FFA and PPA definitions used the same criteria as those used in our previous study and detailed description of region of interest (ROI) definition can be seen in Le et al., (under review). The FFA was visually defined from the Face > Object+Scene contrast (for participants without the Object condition, the Face>Scene contrast was used instead). The PPA was visually defined from the Scene > Object+Face contrast (for subjects without the Object condition, the Scene > Face contrast was used instead). Each FFA and PPA was a 5 mm sphere around the individually defined FFA and PPA peak coordinates (see Table 3.1 and 3.2 and Figure 3.2A for an summary ROI combining all the subjects' individual ROIs).

The left MFG was defined by visualization using the Non Select > Select contrast (as described above, this consisted of Remember Both > Remember Face+Remember Scene) of the delay period activity from the working memory task. To define the MFG in individual subjects, the left MFG cluster was extracted from the group level Non Select > Select contrast during the delay period with a threshold of $p < 0.05$ for *Experiment 1*, and a threshold of $p < 0.001$ for *Experiment 2*. A threshold of $p < 0.05$ was used in *Experiment 1* because it was necessary to obtain a large enough cluster to use as a mask at the individual level (105 voxels in *Experiment 1* compared to the 127 voxels in *Experiment 2*). The group clusters were then used as masks at the individual subject level to select individually defined left MFG coordinates. For each subject, the Non Select > Select contrast was masked with the group left MFG cluster and a 5 mm spherical ROI was created around the peak coordinate of each individual that fell within the mask (see Table 3.3). For both experiments, subjects with no significant activation at $t > 2.3$ (3 subjects in *Experiment 1*, 3 subjects in *Experiment 2*) used the average coordinates based on all subjects who did have significant activation (see Table 3.3 and Figure 3.2B for an summary ROI combining all the subjects' individual ROIs).

As there was no group level cluster large enough to use as a mask at a threshold of $p < 0.05$ for the left FEF, left PPC and Precuneus in *Experiment 1*, we defined a set of seeds in the left FEF, left PPC and precuneus

based on the Non Select > Select contrast for datasets from *Experiment 2* only. First a group cluster in the left FEF (thresholded at $p < 0.05$ with a 20mm boundary box to restrict it to the FEF), the left PPC (thresholded at $p < 0.01$ with a 20 mm boundary box to restrict the activation to within the PPC) and the Precuneus (threshold at $p < 0.01$ with a 20 mm boundary box to restrict the activation to within the Precuneus) was used to mask activation at the individual level. Different cluster thresholds were used to create masks for each brain region to restrict the number of voxels within the group mask to be between 127 and 162 voxels to allow for spatial variation in individual ROI locations). For each subject, the Non Select > Select contrast was masked with the group's FEF, PPC and Precuneus clusters and a 5 mm spherical ROI was created around the peak coordinate for each individual that fell within the mask (see Table 4). Subjects with no significant activation at $t > 2.3$ (6 subjects for FEF, 6 subjects for PPC, 5 subjects for Precuneus) used the average coordinates based on the average of all subjects who did have significant activation at $t > 2.3$ (see Figure 3.2B for an summary ROI combining all the subjects' individual ROIs).

To examine thalamic connectivity with these cortical regions, we chose two left and right thalamic masks from Behrens and colleagues [67] available through the anatomy toolbox (<http://www.fz-juelich.de/>) to use as seeds in our functional connectivity analyses. Thalamocortical connectivity was examined for ipsilateral thalamus seeds only. Behrens and colleagues divided the thalamus into 7 subsections based on diffusion tensor imaging (DTI) connectivity from 7 cortical regions, the prefrontal cortex, premotor cortex, motor cortex, somatosensory cortex, parietal cortex, temporal cortex and visual cortex. As our task involves selective maintenance of visual stimuli in working memory, we chose to focus on the prefrontal and parietal subdivisions of the thalamus, corresponding to regions of the thalamus that should include the mediodorsal nuclei and pulvinar nuclei. For all following analyses, the prefrontal subsection of the thalamus will be labeled 'thalamus (prefrontal)' and the parietal subsection of the thalamus will be labeled 'thalamus (parietal)' (see Figure 3.2C). As a comparison thalamic region, we combined the motor and somatosensory subsections of the thalamus into a control thalamic region. Future references to this region will be referred to as thalamus (control).

Functional connectivity analyses

Functional connectivity was examined with psychophysiological interactions (PPI) using the gPPI toolbox (Ref. [111]; <https://www.nitrc.org/projects/gppi>). For the PPI analysis, a GLM was constructed for each participant that included a regressor for the Stimulus (2 sec), Cue+Delay modelled as a 10 sec boxcar function, and Probe (1 sec) (all further references to delay period connectivity refer to the Cue+Delay period of the trial) for each of the three conditions (Remember Face, Remember Scene and Remember Both). For the generalized PPI (gPPI) analysis, time series were extracted from seeds in the thalamus (prefrontal), thalamus (parietal), thalamus (control) and MFG (for cortico-cortical analysis). These time series were then entered as an interaction term for the events and conditions entered into the GLM constructed for PPI. Beta values were extracted from the interaction contrast images and compared across our three conditions for each ROI.

Representational Similarity Analysis

We used Representational Similarity Analysis (RSA) as a measure of neural representation in the FFA and PPA during the delay and probe periods of the task. RSA compares a second-order correlation between a model representational dissimilarity matrix (RDM) and neural activation pattern based RDM [108]. Our model RDM was constructed to maximize dissimilarity between trials with relevant stimuli in different visual categories and minimize dissimilarity between trials with relevant stimuli in the same visual category. RSA is typically run to examine the visual categories within a feature space, our model was designed only to examine two visual categories, so our RSA examined the degree of categorical representation seen in the FFA and PPA. We based our neural RDMs for the FFA and PPA on the dissimilarity of spatial activation pattern (beta estimates across voxels) for all Remember Face and Remember Scene trials such that each subject's' neural RDM was constructed from each trial's dissimilarity, calculated as $1-r$ (r is the Pearson's correlation of voxel betas), with every other trial. First we constructed a GLM modelling each event

(stimulus, cue, delay and probe) of each trial convolved to a HRF separately, resulting in a beta value for each event of each trial at each voxel. We extracted the beta values for the Remember Face and Remember Scene trials at the delay and probe and created separate RDMs for the FFA and PPA for each event. This resulted in 4 neural RDMs per subject which we correlated separately with our model RDM (using Spearman's correlation). To investigate if increased thalamic connectivity with the FFA or PPA during the preferred compared to non-preferred conditions improve representation of preferred stimuli when relevant, we correlated the fisher z transformed correlation value resulting from the correlation of our model RDM with each region's neural RDM with our PPI results for thalamic connectivity with the FFA and PPA.

Path Analyses

To directly compare cortico-cortical and cortico-thalamo-cortical connectivity in response to differing task demands, we used path analysis to model direct cortico-cortical paths from the left MFG to the right FFA and PPA, and the indirect paths through the right thalamus (prefrontal). Path analysis was run with the Lavaan package (<http://lavaan.ugent.be/>) in R (<https://www.r-project.org/>) to examine the mediating effect of the thalamus on connectivity between prefrontal and visual association regions during the Remember Face and Remember Scene conditions. Path analysis solves a set of simultaneous regression equations that theoretically establish the relationship between multiple variables according to a specific model. The trial by trial activation pattern within each ROI was used to define regression equations related to a region's pattern of activation with the patterns of regions connected to it. The simultaneous equations were solved via maximum likelihood to calculate the strength of the interactions between connected regions (path coefficients). Standardized path coefficients can be interpreted as partial correlation or regression coefficients that convey assumptions about the directionality of interactions between brain regions. Model fit was examined via (1) X^2 statistic, degree of freedom and p-value (2) root mean square estimation of approximation (RMSEA) and the 90% Confidence Intervals, an acceptable RMSEA below 0.06 is

considered acceptable (3) Comparative Fit Index, a value greater than 0.90 is considered acceptable fit, and above 0.95 is considered good fit, and (4) the Standardized Root Mean Square Residual (SRMR), a value below 0.09 is considered a good fit [112].

Individual trial betas from the delay period of the Remember Face and Remember Scene trials were extracted from the left MFG, right thalamus (prefrontal), right FFA and right PPA. Trial betas were concatenated across subjects to estimate path coefficients. A model was constructed with direct paths from the left MFG to the right FFA and right PPA, and indirect paths from the left MFG through the right thalamus (prefrontal) to the right FFA and right PPA, accounting for covariation between the right FFA and right PPA (see Figure 3.9). Remember Face and Remember Scene trials were used as a grouping variable, grouping the Remember Face trials and Remember Scene trials separately such that path coefficients can be calculated for each condition. This allows us to compare the path coefficients for the direct and indirect paths between the left MFG to the right FFA and PPA for Remember Face and Remember Scene conditions.

Results

Behavioral results

There was no significant difference in d' ($F(2,64) = 1.146, p > 0.1$) between the 3 conditions (Remember Face: 2.54 ± 0.61 ; Remember Scene: 2.37 ± 0.54 ; Remember Both: 2.46 ± 0.73). Though there was a significant difference in reaction time (RT) ($F(2,64) = 32.325, p < 0.001$) between the 3 conditions (Remember Face: 920 ± 224 ; Remember Scene: 951 ± 237 ; Remember Both: 1013 ± 250), showing that the informative cues facilitated probe recognition responses (see Figure 3.1B). Selectivity benefit refers to the reaction time advantage seen when reducing 2 items in memory to 1 item. Selectivity benefit is calculated as *Remember Both RT (face/scene probe trials only) - Remember Face/Scene (RT)*. Selectivity benefit was significant for both Remember Face ($t(32) = 4.475, p < 0.001$) and Remember Scene ($t(32) = 5.400, p < 0.001$) but there was no significant difference between them ($t(32) = -1.065, p > 0.1$).

Activation changes associated with the working memory conditions

Univariate results from the working memory task have previously been reported in Le et al., (under review) and Oh & Leung (2010). In accordance with our previous analysis, for both *Experiment 1 and 2*, the Remember Scene > Remember Face contrast showed significant increases in the left and right parahippocampal place area (PPA) during the post-cue delay ($p < 0.05$, FDR corrected). For *Experiment 2* the Remember Face > Remember Scene contrast also showed activation in the left fusiform face area (FFA) during the post-cue delay ($p < 0.001, k > 9$, uncorrected), showing that our design was successful at evoking category selective activation in the FFA and PPA. Only *Experiment 2* showed significant load related increases during the delay period in the left MFG, FEF, PPC and precuneus in the Non Select > Select contrast ($p < 0.05$, FDR corrected). *Experiment 1* did not show expected load related increases in these regions, which may be due to a smaller sample size of only 12 subjects, though a one-way ANOVA showed

differential activity to the cue in the left MFG and SPL (see[101]). Both the left and right thalamus (prefrontal) showed a significant difference between the three conditions ($F(2,64)=5.82$, $p<0.01$ and $F(2,64)=5.53$, $p<0.01$ respectively), with significantly greater activation in the Remember Face compared to Remember Both condition (left thalamus (prefrontal): $t(32)=3.98$, $p<0.001$; right thalamus (prefrontal): $t(32)=3.55$, $p<0.001$). The left thalamus (prefrontal) showed a trend towards greater activation in the Remember Scene compared to the Remember Both condition ($t(32)=1.99$, $p=0.055$), and the right thalamus (prefrontal) showed a trend towards a significant difference between Remember Face and Remember Scene ($t(32)=1.92$, $p=0.064$). There was no significant difference in amplitude between three conditions in the left and right thalamus (parietal) ($F(2,64)=1.34$, $p>0.1$ and $F(2,64)=0.25$, $p>0.1$ respectively) (see Figure 3.2D). There was also no significant difference in amplitude between three conditions in the left and right thalamus (control) ($F(2,64)=0.06$, $p>0.1$ and $F(2,64)=0.10$, $p>0.1$ respectively).

Thalamo-cortical connectivity during selective maintenance of Faces and Scenes

To examine the functional connectivity between the thalamus, visual association and prefrontal areas, we used the prefrontal and parietal subdivisions of the right thalamus [67] as seeds in PPI analyses. We extracted the beta values from individually defined FFA and PPA ROIs in the Remember Face, Remember Scene and Remember Both conditions from the PPI analysis. The thalamus (prefrontal) showed significant differences in connectivity with the PPA across the three working memory conditions ($F(2,64)=6.446$, $p<0.1$), and in the direct comparison of the Remember Scene and Remember Face conditions ($t(32)=3.048$, $p<0.01$) as well as the Remember Both>Remember Face contrast ($t(32)=2.137$, $p<0.05$) and a trend towards a significant difference in the Remember Scene>Remember Both contrast ($t(32)=1.845$, $p=0.074$). The connectivity between the thalamus (prefrontal) subsection and the FFA showed a significant difference across conditions ($F(2,64)=3.145$, $p<0.05$), and the direct comparison of the Remember Scene and Remember Face conditions ($t(32)=2.605$, $p<0.05$) (see Figure 3.3A). The thalamus (parietal) showed a

similar pattern but no significant effects. No significant differences were seen in connectivity between conditions with the PPA ($F(2,64)=1.802$, $p>0.1$), nor was the direct comparison between Remember Scene and Remember Face significant ($t(32)=1.652$, $p>0.1$). The thalamus (parietal) with FFA also did not show a difference between conditions ($F(2,64)=0.982$, $p>0.1$) or a difference between Remember Face and Remember Scene ($t(32)=0.989$, $p>0.1$) (see Figure 3.3B). The thalamus (control) connectivity with the PPA showed a significant difference between conditions ($F(2,64)=3.539$, $p>0.05$) but no difference between Remember Scene and Remember Face conditions ($t(32)=1.447$, $p>0.1$). The thalamus (control) connectivity with the FFA did not show a difference between conditions ($F(2,64)=1.81$, $p>0.1$) or a difference between Remember Face and Remember Scene ($t(32)=0.746$, $p>0.1$).

Functional connectivity between dorsolateral prefrontal cortex and visual association cortices during selective maintenance of Faces and Scenes

To examine if the prefrontal cortex showed significant differences in its functional connectivity to the visual association regions in our datasets, we did a PPI analysis with individually defined left MFG seeds based on the Non Select > Select contrast during the delay period of the univariate analysis. The left MFG connectivity with the right PPA showed significant differences between conditions ($F(2,64)=3.726$, $p<0.05$), with significant differences between Remember Scene and Remember Face condition ($t(32)=2.558$, $p<0.05$). The left MFG connectivity with the right FFA showed a trend towards significant difference between conditions ($F(2,64)=2.43$, $p=0.096$), but did show a significant difference between Remember Face and Remember Scene conditions ($t(32)=2.088$, $p<0.05$) (see Figure 3.3C).

Functional connectivity from thalamus to frontoparietal regions

As frontoparietal regions are known to mediate load related activity during working memory tasks, we examined connectivity from the left thalamus (prefrontal) and thalamus (parietal) to the individually defined left MFG, FEF, PPC and Precuneus ROIs (see Figure 3.4). The left thalamus was examined in this analysis as we were interested in examining the ipsilateral connectivity patterns and our cortical ROIs, except the Precuneus, were from the left hemisphere. The thalamus (prefrontal) showed significant differences between conditions in the PPC ($F(2,40)=3.753$, $p<0.05$) and precuneus ($F(2,40)=6.515$, $p<0.01$), a trend towards a significant difference between conditions with the MFG ($F(2,64)=2.502$, $p=0.090$), but not with the FEF ($F(2,40)=1.643$, $p>0.1$). The thalamus (prefrontal) showed differences in connectivity between Remember Face and Remember Scene conditions with the PPC ($t(20)=2.847$, $p<0.01$, remains significant after bonferroni correction at $\alpha=0.016$) and Precuneus ($t(20)=2.501$, $p=0.021$, not significant after bonferroni correction at $\alpha=0.016$), but not the MFG or FEF ($-1.6<t's<1.6$, $p's>0.1$). The Remember Both and Remember Scene conditions showed significant differences in connectivity with the MFG ($t(20)=2.356$, $p=0.025$, not significant after bonferroni correction at $\alpha=0.016$), PPC ($t(20)=2.231$, $p=0.037$, not significant after bonferroni correction at $\alpha=0.016$) and Precuneus ($t(20)=2.897$, $p<0.01$, remains significant after bonferroni correction at $\alpha=0.016$), and a trend towards significance in the FEF ($t(20)=-1.824$, $p=0.083$). The Remember Both and Remember Face conditions showed a trend towards a significant difference in the Precuneus ($t(20)=1.892$, $p=0.073$) and no significant differences in the MFG, PPC or FEF ($t's\leq\pm 1.6$, $p's>0.1$). The thalamus (parietal) showed a trend towards a significant difference between conditions with the Precuneus ($F(2,40)=2.938$, $p=0.053$), but no significant difference in connectivity between conditions with the MFG, PPC or FEF ($F's<2$, $p's>0.1$).

Categorical representation in the FFA and PPA

RSA was applied for both the delay and probe period of the task and for both the FFA and PPA by conducting a second level correlation between the neural RDM based on trial by trial dissimilarity of Remember Face and Remember Scene trials and the model RDM which predicts minimum dissimilarity within condition (Remember Face trials with Remember Face trials and Remember Scene trials with Remember Scene trials) and maximum similarity across condition (Remember Face trials with Remember Scene trials) (see Figure 3.5A). Significance was tested through permutation for each subject and a binomial test was conducted for each condition, all neural RDMs (FFA and PPA at delay and probe) were significantly correlated with model RDMs at $p < 0.05$, FFA at probe, PPA at delay and PPA at probe remained significant at a threshold of $p < 0.01$ (signifying significance after bonferroni correction).

Thalamocortical connectivity in association with categorical representation in FFA and PPA

To examine the association between thalamocortical connectivity and neural representation of face and scene working memory in the FFA and PPA, we calculated the association between RSA values in the FFA and PPA with thalamocortical connectivity from the PPI analysis. There was no significant correlation between thalamus (prefrontal and parietal)-PPA connectivity and RSA values within the PPA at delay or probe ($-0.2 < r's < 0.2$, $p's > 0.1$) (see Figure 3.5B). There was a trend towards significant negative correlation between thalamus (parietal)-FFA connectivity and RSA values at probe in the FFA ($r = -0.31$, $p = 0.082$). There was no other significant correlation between the thalamus (prefrontal or parietal)-FFA connectivity and RSA values at delay or probe in the FFA ($-0.2 < r's < 0.2$, $p's > 0.1$) (see Figure 3.5C). We also examined the association between RSA values in the FFA and PPA and cortico-cortical connectivity from the PPI analysis. There was a significant positive correlation between MFG-PPA PPI for the Scene > Face contrast and probe period RSA in the PPA ($r = 0.46$, $p < 0.01$) but no significant correlation between MFG-PPA PPI for Remember Scene > Remember Face contrast and delay period RSA in the PPA ($r = -0.16$, $p > 0.1$) or

between MFG-FFA PPI for the Remember Face > Remember Scene contrast and delay or probe period RSA in the FFA ($-0.3 < r's < 0.3$, $p's > 0.1$) (see Figure 3.6).

Thalamocortical functional connectivity correlates with behavior

We further examined whether thalamocortical connectivity was associated with individual differences in task performance, by correlating the thalamus (prefrontal) and thalamus (parietal) PPI with the FFA in the Remember Face>Remember Scene PPI contrast and PPA in the Remember Scene>Remember Face PPI contrast with accuracy (d') and Selectivity Benefit in the Remember Face and Remember Scene conditions. There was a significant positive correlation between both the thalamus (parietal) and thalamus (prefrontal) PPI with the FFA in the Remember Face>Remember Scene contrast and Selectivity Benefit in the Remember Face condition ($r=0.660$, $p<0.001$ and $r=0.434$, $p=0.011$, remains significant with bonferroni correction at $\alpha=0.0125$). There was no significant correlation between the thalamus (parietal) or thalamus (prefrontal) PPI with the PPA in the Remember Scene>Remember Face condition with Selectivity Benefit in the Remember Scene condition ($-0.3 < r's < 0.3$, $p's > 0.1$). There was no significant correlation between the thalamus (parietal) and thalamus (prefrontal) with the FFA in the Remember Face > Remember Scene contrast and the PPA in the Remember Scene > Remember Face contrast with the d' in either the Remember Face or Remember Scene conditions ($-0.3 < r's < 0.3$, $p's > 0.1$) (see Figure 3.7). We also tested the association between cortico-cortical connectivity and Selectivity Benefit. We found that the MFG-FFA PPI in the Remember Face > Remember Scene contrast was significantly associated with Selectivity Benefit in the Face condition ($r=0.44$, $p<0.05$) but not between the MFG-PPA PPI in the Remember Scene > Remember Face contrast and Selectivity Benefit in the Scene condition ($r=0.10$, $p>0.1$). We further tested the association between FFA and PPA amplitude difference in the Remember Face > Remember Scene and Remember Scene > Remember Face contrasts respectively with Selectivity Benefit in the Face and Scene conditions. We found that FFA amplitude was positively associated with Selectivity Benefit in the Face

condition ($r=0.47$, $p<0.01$), but PPA amplitude was not associated with Selectivity Benefit in the Scene condition ($r=-0.01$, $p>0.1$) (see Figure 3.8).

Task dependent thalamic mediation of cortico-cortical connectivity

Thalamic mediation of connectivity between the MFG and FFA or PPA during Remember Face and Remember Scene trials was examined via path analysis. The model tested examined direct and indirect connectivity from the MFG to FFA and PPA in the same model. Based on all parameters of model fit, our model was a just identified model, with a X^2 of 0, RMSEA of 0, CFI model fit of 1 and SRMR of 0. Just identified models mean that all parameters are uniquely determined and provide a good solution to fit the data. As the model was a good fit for the data, path coefficients were further tested to examine the significance of direct and indirect paths from the MFG to FFA and PPA via the thalamus (prefrontal) (see Figure 3.9).

The direct MFG→FFA path was significant for both Remember Face and Remember Scene conditions (path coefficients 0.218 and 0.154 respectively, significant at $p<0.001$), but showed no difference between conditions (difference in path coefficient of 0.065, $p>0.1$). Comparatively, the direct MFG→PPA path was significant in the Remember Scene condition (path coefficient of 0.166, $p<0.001$) but not the Remember Face condition (path coefficient of 0.045, $p>0.1$) and showed a significant difference between conditions (difference in path coefficient -0.121, $p<0.05$).

The indirect MFG→Thalamus (prefrontal)→FFA path was significant for both Remember Face and Remember Scene (path coefficients 0.102 and 0.056 respectively, $p<0.001$), with no significant difference between conditions (difference in path coefficient of 0.027, $p>0.1$). Similarly, the indirect MFG→Thalamus (prefrontal)→PPA path was significant for both Remember Face and Remember Scene (path coefficients

0.104 and 0.077 respectively, significant at $p < 0.001$), with no significant difference between conditions (difference in path coefficient 0.046, $p > 0.1$).

Discussion

We investigated whether thalamocortical connectivity with visual association regions preferring face or scene stimuli varies as a function of the task relevance of their preferred stimuli. PPI analysis of thalamic connectivity with the FFA and PPA both showed that connectivity was stronger when their preferred stimuli were relevant, compared to when it was not. Consistent with existing literature [103], cortico-cortical connectivity between the prefrontal and visual association regions showed similar task dependent connectivity changes. To better contrast task dependent thalamocortical and cortico-cortical connectivity, we constructed a path model which includes the direct cortico-cortical paths between MFG and FFA/PPA, and an indirect path through the thalamus. We found that while both the direct and indirect paths significantly contributed to FFA and PPA activation, only the direct MFG-PPA path was significantly modulated by condition (Remember Scene > Remember Face). Further analysis of thalamocortical connectivity found that it was not associated with the categorical representation of faces and scenes, as measured by RSA [108], though cortico-cortical connectivity between MFG-PPA was associated with categorical representation in the PPA at probe. Thalamus-FFA connectivity did show a positive correlation with behavior, such that subjects who show a greater behavioral benefit of selectively maintaining face stimuli in the Remember Face condition also show greater thalamus-FFA connectivity pattern in the Remember Face > Remember Scene contrast.

Task relevant thalamocortical connectivity

We showed that thalamocortical connectivity to visual regions differ by the task relevance of that region's preferred stimulus category. The thalamus has been proposed to be involved in attention gating [113–115], and in synchronization of cortical networks [25,73,116,117]. Neural evidence for attention gating has been seen in the lateral geniculate nucleus (LGN) and refers to the release of relevant information while inhibiting irrelevant information [114]. Neuroimaging studies also show that pulvinar activations vary in

correspondence to attention requirements [76,118,119], and a study using MVPA has shown that it is possible to classify features and locations in the thalamus only when they are attended [77]. These results have all been explained by the attention gating hypothesis, but are all consistent with the synchronization hypothesis, which proposes that the thalamus increases synchronization between networks of cortical neurons that would enhance activity to task relevant (attended) stimuli [73]. The defining characteristic of the synchronization model is that it stresses the importance of thalamocortical connectivity in mediating task relevant information within the cortex. Our study extends the literature by showing that the previously shown task dependent differences in thalamic activation and classification accuracy, which has been taken as a sign of attention gating is also seen in thalamocortical connectivity, suggesting that the synchronization effects of the thalamus on cortical activity may also play a role in selection in working memory. Our data does not differentiate between these two theories of thalamic function, and future studies might be designed with an interference condition that would help tease these two theories apart.

Differential thalamocortical connectivity between the thalamus and the FFA is also positively associated with the behavioral advantage resulting from selectively maintaining only face stimuli. The association between thalamocortical connectivity and a behavioral measure of successful gating support that thalamocortical connectivity may have an important role in information gating (though it is also consistent with the synchronization theory). The lack of an association with thalamus-PPA connectivity and a selectivity benefit of scene stimuli indicates that this effect may be sensitive to regional differences in connectivity. There are documented differences between FFA and PPA responses when memorizing face and scene stimuli. It has previously been shown that the PPA, but not the FFA shows sustained BOLD activation during the delay period of working memory tasks [101], though it is possible to classify whether Faces or Scenes are relevant from both the PPA and FFA [38] and Le et al., under review). This indicates that delay period PPA activation is more robust, and may not be as sensitive to the thalamus either enhancing relevant information (as predicted by the synchronization model) or inhibiting irrelevant information (as predicted by the gating model). This lack of sensitivity may translate to a dissociation

between thalamocortical connectivity and behavior, with PPA activation itself sufficient to modulate behavior, or through its connectivity with other cortical regions.

Comparison of thalamocortical with cortico-cortical connectivity

Consistent with previous literature [48,50,51,103], our prefrontal seed (located in the left MFG) showed similar connectivity patterns with visual association regions as seen in the thalamus. Previous reports have proposed that this indicates that the prefrontal cortex has a top-down effect on activity in visual association regions in accordance with task goal [14,17,120]. Our results show that the thalamus appears to have a similar role during selective maintenance. We compared thalamocortical and cortico-cortical connectivity in a unified path model and showed that while the thalamus showed significant mediation effects on MFG-PPA and MFG-FFA connectivity, this mediation did not appear to be task dependent. Only MFG-PPA connectivity is significantly modulated by task in the model.

The path analysis results appear to contradict the PPI results, and suggests that thalamocortical connectivity does not show task dependent variation independent of cortico-cortical connectivity. It is possible that when attention is modulated by higher order category, thalamocortical connectivity is less sensitive than cortico-cortical connectivity. However, our findings may be biased by our use of trial betas rather than timecourses to fit our path model. Beta series is primarily a measure of coactivation, as it does not explicitly test temporal associations. Compared to beta series correlations, PPI uses timecourse information to obtain connectivity measures, and while it does not explicitly model temporal associations, PPI is likely to be more sensitive to changes of smaller temporal scales as timecourse data provides a sample every 1.5-2 seconds, compared to one sample per trial. Theories of thalamocortical connectivity stress importance of timing [20,25,73,121–123], so thalamocortical connectivity may be less sensitive than cortico-cortical connectivity to category level changes at the scale of trials.

Thalamocortical connectivity association with stimulus representation

Our results do not support that thalamocortical connectivity influences behavior through enhancing categorical representation of stimuli in the visual cortex. We found no association between thalamocortical connectivity and stimulus representation, as measured by the degree to which the FFA and PPA show categorical representation of faces and scenes calculated through RSA [108]. Disruption of thalamic neural activity has been shown to lead to a relative reduction of neural activity for attended compared to unattended stimuli in neurons within the visual cortex that select for specific stimuli [26]. Previous studies have shown that it is possible to classify individual stimuli from the pulvinar in a task dependent manner [77], suggesting that the pulvinar shows representation for attended, but no clear representation of unattended stimuli. If the pulvinar maintains representation of individual stimuli, it is possible that thalamocortical connectivity may also show correlations with individual stimuli, but not higher order stimuli categories. Our RSA was restricted to only be able to differentiate between the two categories of stimuli we used rather than being able to explore representational similarity across a larger stimulus space, which is the key advantage of RSA. Our current task does not allow us to test representation of individual stimuli as all images were trial unique. Future studies may be interested in investigating the association between thalamocortical connectivity and specific, rather than categorical stimuli. It would also be beneficial to include a behavioral measure of representation fidelity, such as a precision measure [44,124].

Thalamocortical connectivity for thalamic subsections

The thalamus is composed of multiple nuclei with different patterns of connectivity. The MD and pulvinar nuclei particularly have been implicated in visual and visuospatial working memory and attention [19,20,91–93,125]. While our data did not allow us to anatomically define the MD and pulvinar, we used parcellations of the thalamus based on structural connectivity to examine differences in functional thalamocortical connectivity. We chose two region of the thalamus, one showing structural connectivity

with the prefrontal cortex and the other with parietal cortex [67]. Our results indicate that the pattern of connectivity between the thalamus and visual regions is similar for the prefrontal and parietal subsections of the thalamus, though effects were stronger for the prefrontal subsection of the thalamus. In contrast, the association between thalamocortical connectivity and behavior was greater for the parietal subsection of the thalamus. This indicates that there may be differences between the different regions of the thalamus. There is extensive literatures suggesting that the pulvinar is associated with selection externally presented stimuli [20,26,74,76]. In contrast, the MD is known to show persistent neural activity during delay periods in visuospatial working memory tasks [91–93]. It is therefore possible that the thalamus (prefrontal) (roughly overlapping with the MD) may be more involved during the delay period while the thalamus (parietal) (roughly overlapping with the pulvinar) may be more involved at the later perceptual stage, perhaps in the late delay or probe. If the pulvinar is involved closer to the behavioral output, it may show a stronger association with the behavior results. Our control thalamic region, composed of the motor and somatosensory subsections of the thalamus showed no difference between Remember Face and Remember Scene conditions, further providing support that fMRI can be used to differentiate between different thalamic regions. More studies with =with greater spatial and temporal resolution are needed to further investigate these differences and try to tease apart the roles of the MD and pulvinar in human visual working memory.

Conclusion

In conclusion, our findings show that thalamocortical connectivity changes in a task dependent manner and that this connectivity may potentially influence behavioral performance. These findings suggest that the thalamus is involved in selection of relevant information, though it does not differentiate between whether the thalamus is involved in gating or in synchronization. We were unable to show any association between thalamocortical connectivity and stimulus representation across subjects, however future studies

investigating trial-by-trial changes should be conducted before rejecting the hypothesis that thalamocortical connectivity influences the fidelity of stimulus representation.

Chapter 4

Study 2: Behavioral modulation of cortico-thalamo-cortical and cortico-cortical connectivity associated with working memory and attention in a visual search task

Background and Rationale

Visual search refers to the ability to locate a target amongst distractors in the visual field, and search performance has long been used as a measure of visual attention [126,127]. It has also been suggested that visual search can involve working memory to flexibly facilitate or inhibit search behaviors [128,129]. The thalamus is known to be involved in working memory and attention [19,20,91–93,125]. A neural model of thalamic function proposes that the thalamus mediates cortico-cortical connectivity between networks of cortical regions and cortical areas in a behaviorally relevant manner [73]. By implementing a visual search task for memorized targets, we tested how trial by trial search efficiency measures is associated with cortico-thalamo-cortical and cortico-cortical connectivity during visual working memory and attention.

Neuroimaging studies have identified a network of cortical regions that are consistently activated during visual search tasks, including the dorsolateral prefrontal cortex (PFC), frontal eye fields (FEF), superior parietal lobule (SPL) and intraparietal sulcus (IPS), which show increased activation with increased search difficulty [130–134], typically manipulated by the varying similarity between search targets and distractors. A few studies have also examined cortico-cortical connectivity during visual search, finding increases in connectivity between frontal, parietal and visual regions under more difficult search conditions [135,136]. Increased search difficulty has greater attention requirements as more shifts of attention are necessary find targets. Both covert and overt shifts of attention have been found to involve frontoparietal regions [137–139].

Representations in working memory have been shown to be able to both facilitate and impair visual search [128,129,140]. Cuing search targets prior to visual search can facilitate search if they match the target

[141,142], but impair search if they match the distractors [128,143]. The influence of memory representations on search decreases with increased memory load [144,145] and it is possible that the use features held in memory during search only occurs when those features are maintained at high precision [124]. The facilitation of search by representations in working memory have been associated with increased frontoparietal activation [146,147], as well as increased connectivity between frontoparietal and visual association regions [148]. Comparatively, connectivity between inferior frontal gyrus and superior frontal gyrus has been shown to increase when representations in memory impair search [149]. A study explicitly investigating the association between working memory load and visual search for previewed targets used the contralateral delay activity (CDA) as a proxy of working memory load [150] and found that worse search performance was associated with greater CDA prior to search [151]. These studies all indicate that representations in memory can impact visual search, either positively when features match the target, or negatively when they match distractors. Frontoparietal regions seem to be involved in this interaction between features in memory and visual search.

The thalamus has also shown increased activation with increased search difficulty. Both the pulvinar and MD show linear increases in activation with search difficulty [76]. The pulvinar has shown increased activation when features in memory facilitate search and decreased activation when features in memory impair search [146,147], though there is also conflicting evidence showing that activation in both the pulvinar and MD increase when features in memory matched distractors during search [81]. The pulvinar and MD may be necessary for this cue related facilitation in visual search. Stroke patients with damage to the ventrolateral, pulvinar and MD do not show expected facilitation of search performance when features in memory shared features with search targets [81]. The pulvinar particularly has been hypothesized to be involved in gating for relevant information and filtering out irrelevant [74]. The pulvinar shows increased connectivity with the temporal parietal junction and visual regions when search is facilitated [152]. The greater the thalamocortical connectivity, the lower the behavioral cost of distractors across subjects, supporting the theory that the thalamus is gating information. An open question is whether thalamocortical

connectivity with frontoparietal regions varies with cue related enhancement of visual search. Cortico-cortical and thalamocortical connectivity have also not been directly compared in the context of visual search.

The objective of *Study 2* was to investigate the association between cortico-cortical and cortico-thalamo-cortical connectivity with search performance measurements related to target representation and attention. At delay, we modelled connectivity between the prefrontal (MFG), parietal (PPC) and thalamus as these regions are involved in maintenance of items held in visual working memory [46,47,153–155]. Under this framework the prefrontal cortex exerts top-down influence on parietal regions to enhance representation of memorized items [14,17,120], and the thalamus is proposed to mediate the connectivity between the prefrontal and parietal cortex. At search, we constructed a different model, examining the connectivity between the thalamus, MFG and the FEF, which is known to be involved in covert and overt shifts of attention [156–159]. This model at search assumes that MFG influences activation in the FEF, with the thalamus mediating connectivity between these regions. The MD is known to be extensively interconnected with both the MFG and the FEF [58,160], and thalamocortical connectivity has been shown to be important in overt shifts of attention and eye movements [161].

We hypothesized that (1) during the delay, cortico-cortical and cortico-thalamo-cortical connectivity between the prefrontal, thalamic and posterior parietal regions involved in visual representation should be positively associated with search performance, indicating improved target representation. Further, we hypothesized (2) that during visual search, cortico-cortical and cortico-thalamo-cortical connectivity between the prefrontal, thalamic and premotor regions would be associated with lower search performance, indicating greater search difficulty and increased attention.

Methods

Participants

Fifteen healthy young adults participated in this study (5 females and 10 males; 18-31 years of age, mean = 22.06). Participants were recruited through flyers posted around the Stony Brook University campus. All participants had normal or corrected to normal vision (contact lenses only), no color blindness (as tested by the Ishihara plates test) and had no history of substance abuse, major neurological or psychiatric disorders. Written consent was obtained from all participants in accordance with the Institutional Review Boards at Stony Brook University and participants were compensated monetarily.

Design and Stimuli

Participants did a visual search task with cued targets. Participants were first presented with a *Stimulus* display containing trial unique target image(s) they were instructed to remember for a later visual search task. The Stimulus display was followed by a *Delay* period, then memory was probed in the *Search* display, in which participants were instructed to find which of the 5 objects presented was a memorized target image (see Figure 4.1 for schematic).

The task contained 2 conditions, determined by the number of target objects presented during the Stimulus display. In the 1-Target condition, two of the same image was presented while in the 2-Target condition, two different images were presented. In the 2-Target condition, participants were aware that only one of the targets would be present in the Search display. Two images were always presented during in the Stimulus display. The image was repeated in the 1-Target condition in an attempt to equalize the visual aspects of Stimulus display. The Search display consisted of 5 items, one of which was always a target.

Every trial started with a 2 s fixation, followed by a 3 s Stimulus presentation, a 9 s Delay and the 3.5 s Search display. After the onset of the Search display, participants were required to look at the target and press a button with their right or left index finger (counterbalanced across subjects). The subjects were able

to make a response anytime within the 3.5 s Search display. Between trials, there was a variable inter-trial interval (ITI) consisting of 10.5, 12.5 or 14.5 s. Trials were arranged in 8 runs, each of which consisted of 12 intermixed trials. Each run had 6 trials from each condition, in pseudorandom order. There were a total of 48 trials in each of the two conditions. All trials were counterbalanced within and across runs. The order of runs was counterbalanced across subjects. All runs were 6 minutes long.

Stimuli were randomly chosen from the Hamerra collection, with no restriction on object category. No objects from the same basic category were presented in the same search display. Images were an average size of 1.4° visual angle and were the same size in both the preview and search display. In the stimulus display, target images were presented 3° visual angle away from central fixation. In the 5-object search display, the center of each image was arranged randomly in a circle with a radius of 5° relative to central fixation. We calculated the *Preview Saliency* of search targets during the Stimulus display to gain a measure of how salient the to be remembered items were. First the saliency of each Stimulus display was calculated using the Itti & Koch model of saliency [162] based on code from (<http://www.klab.caltech.edu/~harel/share/gbvs.php>) in matlab. Then a 200 x 200 pixel mask was placed around the centroid of each target item in the Stimulus display and the *Preview Saliency* was calculated as the mean saliency within both masks, resulting in a saliency value per Stimulus display screen (i.e. per trial). We also calculated the *Target Saliency* in the Search display, which is a measure of how salient the target object is in relation to the distractors in the search display. We first calculated the saliency of each trial's Search display, then masked each of the 5 items in the search display with a 200x200 pixel mask. For each item, an average saliency value was calculated by taking the mean saliency within the mask of that object. *Target Saliency* was calculated by taking the proportional saliency of the target item (target saliency/total saliency of all 5 items) and subtracting the average of the distractor proportional saliency (distractor saliency/total saliency of all 5 items, averaged across the 4 distractors).

A behavioral screening session preceded scanning. Participants were screened for ease of calibration on the eye-tracker, due to it being more difficult to calibrate on the eye-tracker in the scanner. A practice session

followed calibration, including 20 trials of the same paradigm. No image used in the practice trials was used in the experimental task.

Eye-movement data acquisition and analysis of visual search behavior

Eye-movements were collected from the left eye throughout the task with an EyeLink 1000 eye-tracker (SR research, Canada) with a sampling rate of 1000 Hz and an average spatial accuracy of 0.5°. Saccades were defined as eye movements with a motion of greater than 0.15°, velocity greater than 30°/sec, and acceleration greater than 8000°/sec. Fixations were defined as eye movement that fell below the saccade thresholds for at least 50 ms. Blinks were detected when there was partial occlusion of the pupil followed by loss of pupil. For each run, the eye-tracker was calibrated by mapping eye position to screen coordinates. Average calibration for all subjects was 0.35°±0.1 (average maximum calibrations scores across subjects was 0.70°±0.19) indicating that gaze location as measured by the eye tracker was on average 0.35° away from the actual gaze location. To maintain precise timing for each trial, no drift correction was done between trials, and due to time constraints, calibration was done on average 3 times per participant, for the first, middle and last runs, or as needed if saccade recording accuracy degraded (based on visual inspection) before the next run.

By recording eye-movements, we are able to examine neural responses associated with more fine grained search behavior. The standard measure of search performance is (1) *Reaction Time* (measured as the time between Search display onset and button press), with faster Reaction Time indicating better search performance. However, Reaction Time includes the time for many different processes, including both finding the search target (indicated by fixating on the target) and recognizing that the item fixated is the target (indicated by a button press). Therefore, we parsed Reaction Time into two parts, the *Time to Target* and *Target Dwell Time*. (2) *Time to Target* refers to the time from search display onset to when the participant first fixates on the target and measures the participant's ability to find the target amongst

distractors. (3) *Target Dwell Time* (calculated as *Reaction Time - Time to Target*) measures the time between when a target is first fixated and when the participant presses the button to respond and is a measure of the time required for individuals to recognize the target and make a response.

Another commonly used measure of search guidance (the ability to guide eye movements based on target representations [163]) is (4) *Initial Saccade Direction*, which measures whether the initial saccade moves in the direction of the target. Initial Saccade Direction is a more stringent measure of search guidance than Time to Target as it gives observers only a couple hundred milliseconds to analyze the search display before making this eye-movement [142]. The Initial Saccade Direction was calculated by dividing the imaginary circle on which the search objects into 5 equal-sized 72° slices, one slice for each item in the search display. Initial saccades that landed within the target slice were considered initial saccades directed at the target and considered accurate, all initial saccades landing outside the target slice were considered inaccurate. Initial Saccade Direction was therefore a binary measure with 1 representing initial saccade in the target direction and 0 representing saccades outside of the target direction. By chance, 1/5 or 20% of the initial saccades should land within the target slice, significantly greater preference for the target direction indicates efficient search.

Finally, Initial Saccade Latency was calculated as the time from search display onset and the initiation of the first saccade. While not a measure of search efficiency per se, Initial Saccade Latency determines how long participants are able to analyze the search display prior to their first eye-movement as well as the time needed to prepare an eye-movement. When analyzed alongside Initial Saccade Direction, which might indicate a speed-accuracy tradeoff in the initial saccade [164]. For calculation of Initial Saccade Latency and Initial Saccade Direction, trials in which Search display onset coincided with a blink, or a saccade (if Initial Saccade Latency was < 50 ms) were excluded from further analysis.

To obtain good and bad performance trials, we did a median split to separate trials with long and short Time to Target and Dwell Time separately for the 1-Target and 2-Target conditions, then we collapsed across 1- and 2-Target trials to compare trials with good and bad performance.

fMRI data acquisition and analysis

Participants laid supine in the scanner and viewed the screen through a mirror mounted on the head coil. Whole brain images were acquired with a Siemens 3T scanner (Siemens, Trio Trim 3 Tesla). First T1-weighted high-resolution 3D images were acquired (TR = 1.9 sec; TE = 2.53; Flip angle = 9°; FOV = 250×250 mm; Matrix = 256×256). Thirty-three T1 weighted slices (3.5mm thickness, 0.5 gap) were collected along the anterior-posterior commissural (AC-PC) line for the in-plane (TR = 300ms; TE = 5; Flip angle = 60°; FOV = 220×220 mm; Matrix = 256×256) and functional images. 1440 volumes of functional images (180 per run) were collected with a T2*-weighted EPI sequence (TR = 2 sec; TE = 30; Flip angle = 80°; FOV = 220×220 mm; Matrix = 72×72). The first 3 volumes were removed for MR signal stabilization.

All images were preprocessed in SPM8 (Wellcome Trust Centre for Neuroimaging, University College London, <http://www.fil.ion.ucl.ac.uk/spm/>). The first 3 volumes of each functional run were discarded to allow T2* signal to reach equilibrium. The remaining functional images were corrected for differences in slice acquisition timing and head motion. A mean EPI image was then generated from the realigned images. T1 weighted inplane structural images were co-registered with the mean EPI image, then MPRage images were coregistered to the T1 weighted inplane structural image. Segmentation was applied to the high resolution T1 structural image and segmented images were normalized to the Montreal Neurological Institute (MNI) template. The same transformation parameters were then applied to all functional images. Finally, all functional images were spatially smoothed with a Gaussian kernel of 6 mm at full-width half-maximum and were high-pass filtered with a cutoff of 1/128 Hz.

Univariate analysis of load differences was examined for each participant, a general linear model (GLM) was constructed which included 3 regressors for each conditions, one for each event in the trial; Stimulus display, mid-Delay (defined as 4.5 seconds after the Stimulus display offset) and Search display. Onset times for each task event was 2 s, 9.5 s and 14 s from the beginning of each trial. The duration of the Stimulus display was modeled with a duration of 3 s, the mid-Delay modeled with a duration of 0 s and the Search display modeled with a duration of 3.5 s. Regressors were convolved with the canonical hemodynamic response (HRF) function. Trial onsets for each load condition were entered as regressors in the GLM. Error trials were modeled with a separate regressor, but were not further investigated. Head motion was corrected by including 6 motion parameters in the x, y, z, roll, yaw and pitch, as well as motion outliers as regressors in the GLM. Motion outliers were defined as volumes with a scan-to-scan motion greater than 0.5 mm in either the x, y or z plane, or 0.01 radians in either the roll, pitch or yaw rotation, using the Artifact Detection Tools (ART) (http://www.nitrc.org/projects/artifact_detect/). Outlier volumes ranged from 0-34% volumes of each run across the final group of participants (mean $4\pm 5\%$). Individual t-maps were generated to show activations corresponding to load (2-Targets > 1-Target) for each event in the trial. A second level univariate analysis was done to investigate blood-oxygen-level-dependent (BOLD) activation in response to load demand (2-Targets > 1-Target) for each event of the trial (Stimulus, Delay and Search) using one sample t-tests. *Initial Saccade Direction* was examined in another univariate GLM due to the binary nature of our Initial Saccade Direction measure. The GLM modeled Stimulus, Delay and Search at the same onsets as those used for the univariate analysis of load. The trials were reorganized into trials where the initial saccade was towards the target slice vs. those where the initial saccade was away from the target slice. Due to modeling requirements, runs where all trials were toward (or all trials were away) from the target slice were removed from the analysis (a total of 3 runs were removed). A second level analysis was done to examine the Initial Saccade Direction towards target > Initial Saccade Direction away from target contrast.

Parametric modulation by search variables was examined by constructing a parametric design per search measure per subject. For each performance measures (Reaction Time, Time to Target, Target Dwell Time, and Initial Saccade Latency), unweighted covariates for the onset times of the task events (Stimulus, Delay and Search) were weighted by the corresponding search performance variable to create a GLM where the task event of interest (Delay or Search display) was modulated by a HRF convolved measure of search performance. This resulted in 8 GLM models per subjects. We collapsed across load condition to examine the overall effect of the search performance. *Another parametric model was constructed with Preview Saliency at Stimulus* to examine regions modulated by saliency of the to be remember items in the Stimulus display.

ROI selection

To examine connectivity from the thalamus, we used masks of the thalamus from Behrens et al [67] analysis of DTI connectivity from the cortical lobes to the thalamus. We chose the right prefrontal and parietal subdivision of the thalamus in Behrens et al., (2003) dataset due to their connectivity with the prefrontal cortex and the rough correspondence with the MD and pulvinar. Future references to the prefrontal subdivision of the thalamus will be referred to as the *thalamus (prefrontal)* and the parietal subdivision of the thalamus will be referred to as the *thalamus (parietal)*.

The right middle frontal gyrus (MFG) and right frontal eye field (FEF) was visually defined from the 2-Target>1-Target contrast during the delay period. To define the MFG in individual subjects, the right MFG cluster was extracted from the group level 2-Target>1-Target contrast during the delay period at $p < 0.01$. This cluster was then used as a mask at the individual subject level to select MFG and FEF coordinates to create individually defined regions of interest (ROIs). For each subject, the 2-Target > 1-Target contrast was masked with the group MFG and FEF clusters and a 5 mm spherical ROI was created around the peak coordinate that fell within the masks. Subjects with no significant activation at $t > 2.6$ used the average

coordinates based on all subjects who did have significant activation (1 subject for MFG and 1 subject for FEF).

A right posterior parietal region was selected from the parametric analysis of Preview Saliency at Stimulus display to select a region within the right PPC that was sensitive to the saliency of the memorized search targets. This Preview Saliency based PPC region overlaps with that seen in the 2-Target>1-Target load contrast. A group cluster was selected from the PPC that was positively associated with Saliency during the Stimulus display at $t > 2.6$ (corresponding to $p < 0.01$). This cluster was then used as a mask at the individual subject level to select individually defined PPC coordinates based on a positive association with Preview Saliency. A 5 mm spherical ROI was created around the peak coordinate that fell within the group PPC mask. Subjects with no significant activation at $t > 2.6$ used the average coordinate based on all subjects who did have significant activation (2 subjects).

Functional connectivity analyses

We examined functional connectivity using ROI-ROI beta series correlation analysis [48,51,103,165]. A GLM is generated for each subject with each event in each trial was modelled as a separate regressor, thereby giving us a total of 288 beta values per subject. Even though we modelled all three trial events (Stimulus display, Delay and Search display), we only examined connectivity of Delay period betas. All beta series analyses were motion corrected such that the beta of any trial with motion outliers (scans with scan-to-scan motion greater than 0.5 mm translation or 0.01 radians rotation) between the onset of the Stimulus display and the offset of the Search display were excluded from the analysis.

To examine connectivity differences between conditions, we further separated the Delay period betas into 2-Target trials and 1-Target trials. For each condition, we extracted a mean beta series from the right thalamus (prefrontal) and right thalamus (parietal) seeds and correlated with the rest of the voxels in the brain for the 1 and 2-Target conditions separately. We then extracted fisher z transformed correlation values

(Pearson's r) from the right MFG, FEF and PPC ROIs and a paired-samples t-test was used to compare thalamocortical connectivity between 2-Target and 1-Target conditions.

We further compared thalamocortical connectivity for trials with long (poor performance) and short (good performance) Time to Target and Target Dwell Time measures of search performance. We only examined thalamocortical connectivity for these two search performance measures as together they make up Reaction Time (the most typically used search performance measure), rendering Reaction Time a redundant search measure. We did not examine Initial Saccade Direction, the strictest guidance measure, because the distribution of initial saccades towards the target across subjects was non-normal, with some subjects attaining as high as 80% of initial saccades towards the target and others only 20%.

As we had insufficient trial betas after motion correction, we did not separately examine good and bad performance for 1 and 2-Target conditions.

Path Analysis

The moderation of search performance measures on the mediating effect of the thalamus (prefrontal) on the cortico-cortical connectivity between the MFG and PPC during the Delay and MFG and FEF during Search was investigated by examining the moderated mediation effects in a path analysis with the Lavaan package (<http://lavaan.ugent.be/>) in R (<https://www.r-project.org/>). Two separate path models were constructed replacing thalamus (prefrontal) with thalamus (parietal). Path analysis solves a set of simultaneous regression equations that theoretically establish the relationship between multiple variables according to a specific model. The trial by trial activation patterns within each ROI was used to define regression equations related to a region's pattern of activation with the patterns of regions connected to it. The simultaneous equations were solved via maximum likelihood for the strength of the interactions to connected regions (path coefficients). Standardized path coefficients can be interpreted as partial correlation or regression coefficients that convey assumptions about the directionality of ROI interactions. Moderated mediation

examines the effect of a moderator on the direct and/or indirect paths between variables (regions). In the regression equations, the moderators are expressed as interaction terms in the regression equations.

Individual trial betas from the Delay and Search periods of the task were extracted from the right MFG, FEF, PPC and thalamus. Trial betas from trials with motion (if there was any motion outliers between the onset of the Stimulus display and offset of the Search display), and trial betas with no behavioral values (no Time to Target and Dwell Time measure) were removed. Search performance measures Time to Target and Dwell Time were standardized by calculating the z-values for each subject, and then trials with motion, and trials with no behavioral values were removed. Remaining trial betas and behavioral performance measures were then concatenated across subjects to estimate path coefficients.

To examine the influence of MFG activation on the PPC, as predicted by a recent model of working memory maintenance proposing that the prefrontal cortex exerts top-down influence on parietal regions [14,17], we examined delay period activity by constructing a model with a direct path from MFG → PPC, a mediating effect through the thalamus, an indirect path from MFG → Thalamus → PPC and examined the modulatory influence of Time to Target and Dwell Time on the connectivity between MFG → PPC and Thalamus → PPC (See Figure 4.6). Individual trial beta values from the Delay period, concatenated across subjects was used to fit this model.

To test the influence of the MFG activation on the FEF during Search, we constructed a model with a direct path from MFG → FEF and an indirect path from MFG → Thalamus (prefrontal) → FEF and examined the modulatory influence of Time to Target and Dwell Time on the connectivity from the MFG → FEF and Thalamus (prefrontal) → FEF (See Figure 4.7). Individual trial beta values from the search period, concatenated across subjects was used to fit this model. We included *Target Saliency* as a control variable, by controlling for saliency effects on thalamus and FEF activity.

Model fit was examined via (1) χ^2 statistic, degree of freedom and p-value (2) root mean square estimation of approximation (RMSEA) and the 90% Confidence Intervals, an acceptable RMSEA below 0.06 is considered acceptable (3) Comparative Fit Index, a value greater than 0.90 is considered acceptable fit, and above 0.95 is considered good fit, and (4) the Standardized Root Mean Square Residual (SRMR), a value below 0.09 is considered a good fit [112].

Results

Behavioral Results

Performance was better in the 1-Target compared to 2-Target condition Accuracy ($t(14)=4.89$, $p<0.001$), Reaction Time ($t(14)=8.61$, $p<0.001$), Time to Target ($t(14)=7.48$, $p<0.001$), Target Dwell Time ($t(14)=3.33$, $p<0.01$), and a trend towards a significant difference in Initial Saccade Direction ($t(14)=2.0$, $p=0.065$) between the 1-target and 2-target conditions. There was no significant difference in Initial Saccade Latency ($t(14)=1.64$, $p=0.123$) (see Table 4.1). The decreased search performance on the 2-Target compared to 1-Target condition is consistent with previous studies investigating visual search for multiple targets [166].

Load dependent cortical activations

A direct contrast between the two load conditions during Stimulus display, Delay period and Search display (see Figure 4.2 and Table 4.2) showed that a set of frontal and parietal, as well as visual association regions were more active during the 2-Target>1-Target contrast. The Stimulus display showed above threshold activity (cluster level FDR, $p < 0.05$) in the pre-SMA, FEF, IPL, anterior insula and inferior temporal cortex for the 2 Targets > 1 Target contrast. The Delay period showed significant activation in the pre-SMA, left and right anterior insula ($p<0.05$, FDR corrected) and right IPL ($p<0.001$, $k>9$, uncorrected). These areas are part of a network commonly associated with visual working memory [5,9]; note that the lack of significant MFG activation during the delay may be because remembering 2 random objects does not tax working memory [4]. During Search display, there was significant activity in the pre-SMA, FEF, IPL and left IPS, and anterior insula ($p<0.05$, FDR corrected). There was a large degree of overlap in load dependent activity in the pre-SMA, IPL and anterior insula regions between the Stimulus display, Delay period and Search display.

Search Performance dependent cortical activation

Parametric analyses examining the modulation of BOLD signal by search performance measures (Reaction Time, Time to Target, Target Dwell Time and Initial Saccade Latency) and a univariate comparison of Initial Saccade Direction were conducted to examine brain regions associated with search behavior. All parametric contrast maps were masked to only include regions that were active for the 2-Target>1-Target contrast during the delay period (thresholded at $p<0.05$, uncorrected), so that only regions that are involved in working memory maintenance and sensitive to working memory load were examined.

At Delay, no brain region within the mask was significantly associated with any search performance measure (Reaction Time, Time to Target, Target Dwell Time, Initial Saccade Latency or Initial Saccade Direction). Outside the mask, Reaction Time showed a negative association with BOLD activation in the putamen (-27, 6, 9 significant at $p<0.05$, FDR cluster corrected), such that greater activation in the putamen was associated with lower Reaction Time.

As expected based on previous investigations [130–134], at Search, Reaction Time showed a significant positive association with BOLD signal in the bilateral, MFG, PPC (superior parietal lobule [SPL] and intraparietal sulcus [IPS]), anterior insula, the pre-supplementary motor area (pre-SMA) and the dorsal anterior cingulate cortex (dACC) ($p<0.05$, FDR cluster corrected). Time to Target showed a significant positive association with BOLD signal in the bilateral PPC (IPS and inferior parietal lobule [IPL]), anterior insula, the left MFG and the pre-SMA (See Figure 4.3 and Table 4.3) ($p<0.05$, FDR cluster corrected) indicating that longer Reaction Time and Time to Target was associated with greater BOLD activation in frontoparietal regions.

Load and search performance dependent thalamus activation

There was no difference in amplitude between the 2-Target and 1-Target conditions in either the thalamus (prefrontal) or thalamus (parietal) during the delay (see Figure 4.4A). We also examined whether there was any association between BOLD activation in the thalamus and the search performance measures. Because we wanted to cover the whole thalamus, we combined the 7 bilateral Behrens's masks (which include prefrontal, premotor, motor, somatosensory, parietal, visual and temporal subsections) into one mask of the bilateral thalami. There were 3 significant clusters within the thalamus that showed increased BOLD activation with longer Reaction Time at search (-15, -12, 3; 9, -12, -3 and 24, -21, -6, significant at $p < 0.05$, FDR cluster corrected) (see Figure 4.4B). These clusters were present in both the thalamus (prefrontal) and thalamus (parietal) subsection of the thalamus. There was no significant association between Time to Target, Target Dwell Time, Initial Saccade Latency or Initial Saccade Direction with BOLD activation during the Search period. There was no significant association at the a priori threshold ($p < 0.001$, $k > 9$, uncorrected) between Reaction Time, Time to Target, Target Dwell Time, Initial Saccade Latency or Initial Saccade Direction and BOLD activation during the delay period.

Load dependent thalamocortical connectivity

Load related connectivity during the Delay was compared by separately running beta series correlations with 2-Target and 1-Target trials, then comparing the z-transformed correlation values for 2-Target and 1-Target conditions. There was no significant difference in connectivity between thalamus (prefrontal) and the MFG, FEF or PPC for the 2-Target compared to the 1-Target conditions ($-1 < t's < 1$, $p's > 0.1$). Load related connectivity at Search showed a significant difference between the 2-Target and 1-Target conditions such that the MFG and PPC both showed greater connectivity with the thalamus (prefrontal) in the 1-Target > 2-Target contrast ($t(14) = 2.839$, $p = 0.013$, remains significant after bonferroni correction at $\alpha = 0.0167$ and $t(14) = 2.582$, $p = 0.022$, not significant after bonferroni correction). The FEF did not show a

difference in connectivity with the thalamus (prefrontal) in the 1-Target compared to 2-Target conditions ($t(14)=0.058$, $p>0.1$).

The thalamus (parietal) showed significantly greater correlation with the right MFG at search for the 1-Target compared to 2-Target condition ($t(14)=2.962$, $p=0.010$, remains significant after bonferroni correction at $\alpha=0.0167$). There was no significant correlation between thalamus (parietal) and the PPC, or FEF at search ($-1.5<t's<1.5$, $p>0.1$). There was no significant connectivity between the thalamus (parietal) and the MFG, FEF or PPC at delay ($-1<t<1$, $p>0.1$).

Thalamocortical connectivity associated with search performance

Beta series connectivity was compared for long and short Time to Target and Target Dwell Time during the Delay and at Search. At Delay, Target Dwell Time showed differences in connectivity for the short>long contrast between thalamus (prefrontal) and the inferior frontal gyrus (IFG) (-42, 24, -9) and middle temporal gyrus (MTG) (-54, -14, -15) at Delay ($p<0.001$, $k>9$, uncorrected). At Search, Target Dwell Time showed differences in connectivity for the short>long contrast between thalamus (prefrontal) and the FEF (-33, 6, 39), anterior MFG (-27, 51, 24), lateral occipital/temporal (48, -57, -3), precuneus (3, -75, 24) and the right IPS (27, -78, 30) ($p<0.001$, $k>9$, uncorrected). To test how thalamocortical connectivity to specific frontoparietal regions (FEF, MFG and PPC) differ for short and long Time to Target and Target Dwell Time, we did additional ROI based analysis, results can be seen in Figure 4.5. Only thalamus-PPC connectivity showed differences between long and short Target Dwell Time at delay and search ($t(14)=-2.525$, $p<0.05$, not significant after bonferroni correction at $\alpha=0.0167$) and only thalamus-FEF connectivity showed differences between long and short Time to Target at delay ($t(14)=2.586$, $p=0.022$, not significant after bonferroni correction at $\alpha=0.0167$).

The thalamus (parietal) whole brain beta series connectivity showed connectivity differences in the short>long Target Dwell Time contrast with the MTG (63, -54, 0) at Delay ($p<0.001$, $k>9$, uncorrected)

and with the caudate (0, 15, 6) at Search ($p < 0.001$, $k > 9$, uncorrected). The thalamus (parietal) did not show connectivity differences between long and short Time to Target with any brain region at Delay or Search. The thalamus (parietal) showed a significant difference in connectivity for the short > long Target Dwell Time contrast at Delay with the MFG ($t(14) = 2.327$, $p = 0.035$, not significant after bonferroni correction at $\alpha = 0.0167$) and a trend toward significant difference in connectivity with the PPC ($t(14) = 2.128$, $p = 0.052$). No other ROI showed connectivity differences between long and short Time to Target or Target Dwell Time.

Cortico-cortical and cortico-thalamo-cortical connectivity associated with search performance during the Delay period

To investigate the association between behavior and cortico-thalamo-cortical connectivity at Delay, we constructed a path model examining the modulation effect of the direct MFG-PPC connectivity and modulated mediation effects through the thalamus (prefrontal) (see Figure 4.6). The model was significant ($\chi^2 = 17.7$, $p < 0.01$ with a degree of freedom of 6, a RMSEA of 0.041 with a 90% CI of 0.020 to 0.064, a CFI of 0.979 and a SRMR 0.018). The overall model fit was good [112]. Both the direct path MFG → PPC and indirect path MFG → Thalamus (prefrontal) → PPC were significant (path coefficients of 0.318 and 0.091 respectively, $p < 0.001$). Individual path coefficients are presented in Table 4.4. Time to Target did not show significant modulation of either the direct or indirect path (path coefficients of 0.023 and 0.010 respectively, p 's > 0.1). Dwell Time showed a significant modulation of the indirect path (path coefficient of -0.035, $p < 0.05$) but no significant modulation of the direct path (path coefficient of 0.019, $p > 0.1$).

We tested the same model with thalamus (parietal). The thalamus (parietal) model was significant ($\chi^2 = 22.156$, $p < 0.001$; with a degree of freedom of 6, a RMSEA of 0.049 with a 90% CI of 0.028 to 0.071, a CFI of 0.966 and a SRMR 0.020). The overall model fit was good [112]. Both the direct path MFG → PPC

and indirect path MFG → Thalamus (parietal) → PPC were significant (path coefficients of 0.336 and 0.072 respectively, significant at $p < 0.001$). Individual path coefficients are presented in Table 4.4. Similar to the model with thalamus (prefrontal), Time to Target did not show significant modulation of either the direct or indirect path (path coefficients of 0.024 and 0.013 respectively, $p > 0.1$), while the Dwell Time showed a trend towards a significant modulation of the indirect path (path coefficient of -0.020, $p = 0.086$) and no significant modulation of the direct path (path coefficient of 0.005, $p > 0.1$).

Cortico-cortical and cortico-thalamo-cortical connectivity associated with search performance during the search period

To investigate the association between behavior and cortico-thalamo-cortical connectivity at Search, we constructed a path model examining the modulated mediation effect of behavior direct MFG-FEF connectivity and modulated mediation effects through the thalamus (see Figure 4.7). The model had a $\chi^2 = 35.3$ and was significant at $p < 0.001$ with a degree of freedom of 6, a RMSEA of 0.065 with a 90% CI of 0.046 to 0.087, a CFI of 0.944 and a SRMR 0.014. The overall model fit between good and acceptable [112]. Both the direct path MFG → FEF and indirect path MFG → Thalamus (prefrontal) → FEF were significant (path coefficients of 0.308 and 0.087 respectively, significant at $p < 0.001$). Individual path coefficients are presented in Table 4.4. Time to Target showed a significant modulation of the indirect path (path coefficient of 0.029, $p < 0.05$) but no significant modulation of the direct path (path coefficient of -0.021, $p > 0.1$). Dwell Time did not show significant modulation of either the direct or indirect path (path coefficients of -0.051 and 0.002 respectively, $p > 0.1$).

Similarly, with the thalamus (parietal), the model had a $\chi^2 = 28.650$ and was significant at $p < 0.001$ with a degree of freedom of 6, a RMSEA of 0.058 with a 90% CI of 0.037 to 0.080, a CFI of 0.955 and a SRMR 0.016. The overall model fit was good [112]. Both the direct path MFG → FEF and indirect path

MFG→Thalamus (parietal)→FEF were significant (path coefficients of 0.318 and 0.078 respectively, significant at $p<0.001$). Individual path coefficients are presented in Table 4.4. Time to Target showed a trend towards a significant modulation of the indirect path (path coefficient of 0.028, $p=0.052$) but no significant modulation of the direct path (path coefficient of -0.008, $p>0.1$). Dwell Time showed a trend towards a significant modulation of the direct path (path coefficient of -0.068, $p=0.081$) and no significant modulation of the indirect path (path coefficients of 0.010, $p>0.1$).

Discussion

We examined whether brain activation, thalamocortical and cortico-cortical connectivity was associated with better search performance during the delay, which might suggest that these brain networks are involved in maintaining representations that facilitate visual search. We also examined whether greater search difficulty, requiring more attention was associated with greater brain activation, thalamocortical and cortico-cortical connectivity, suggesting these networks might be involved in visual search relevant attention. In addition to replicating the typical finding of greater frontal, parietal and visual load dependent activations during the search task, we showed that these regions are correlated with search performance across trials. Further, path analysis suggests that search performance measures modulate cortico-thalamo-cortical, but not cortico-cortical connectivity at both delay and search. We found an interaction between Target Dwell Time, a measure of target recognition and cortico-thalamo-cortical connectivity, but not cortico-cortical connectivity between the prefrontal and parietal cortex during the Delay period where subjects are required to maintain the search target. Target Dwell Time interacted negatively with cortico-thalamo-cortical connectivity, with shorter dwell time associated with greater cortico-thalamo-cortical connectivity. However, Time to Target did not interact with either cortico-cortical or cortico-thalamo-cortical connectivity during the delay period of the search task. During Search, Time to Target but not Target Dwell Time interacted with cortico-thalamo-cortical connectivity but not cortico-cortical connectivity, such that longer Time to Target was associated with greater cortico-thalamo-cortical connectivity. These findings suggest that the thalamus mediates cortico-cortical connectivity during both the delay period and at search, with different search performance measures showing differential effects on thalamic mediation of prefrontal-premotor and prefrontal-parietal connectivity.

Differential effects of search performance measures: time to target and target dwell time

Our results show that different search performance measures are differentially associated with thalamocortical connectivity during the delay and at search. Time to target refers to the time between search onset and when the target was first fixated. Behavioral studies indicate that having a good target representation can increase search efficiency, with a shorter time to target [141,142,164,167]. Time to target decreases when a picture target is presented compared to a verbal description of the target (semantic category) [141,164], as well as improving as more visual features of the search target is presented [167]. Time to target improvements from cueing search targets last up to 9 seconds, though behavioral advantage of cueing decline over this 9 second period [164]. These behavioral results suggest that higher fidelity target representations should improve time to target.

During visual search, target dwell times are longer when targets are more difficult to distinguish from distractors [168,169]. Target dwell time is the time between when the target is first fixated and a button press is made. In our study, the only reliably distinguishing feature of the target from the distractors was that the subjects had seen the target object prior to the search display, therefore Target Dwell Time should be a measure associated with recognizing that the fixated object was a previously memorized target.

Thalamocortical connectivity associated with delay period representation of search targets

Representation of visual targets for search are likely maintained in visual working memory prior to and during visual search [151]. Our findings suggest that increased thalamic mediation of connectivity between the MFG and the PPC during the delay is associated with faster recognition of the target at search, but not with finding the target faster. This corroborates the literature as the prefrontal, parietal and thalamic regions have all been implicated in both visual search [76,130–132,170] and visual working memory [46,47,153–155]. Theories propose that, along with visual regions frontoparietal regions form a cortical network that underlies representation of information in memory [14,17,120]. The frontal and parietal regions included

in our model have also previously been shown to have greater activation on trials when stimuli in visual working memory are correctly recognized compared to when they are not [36].

Both the prefrontal and posterior parietal cortex show persistent neural activation during the delay period of visual working memory tasks [153–155], and there is evidence to suggest that representations of memorized stimuli may be stored in these regions [46,47,171,172]. We selected our PPC region based on the modulation of stimulus saliency on this region and the PPC has been shown to be involved in maintaining object features [46,47,171,172]. However, findings from our path analysis do not seem to support that either thalamocortical or cortico-cortical connectivity during the delay period is associated with greater search efficiency (as measured by time to target). This suggests that connectivity between the MFG, thalamus and PPC may not contribute to target representations in a manner that facilitates search efficiency.

In contrast, shortened target dwell time, showing faster target recognition, was associated with greater cortico-thalamo-cortical connectivity. It is possible that the target dwell time more closely linked to visual representation than time to target (as the comparison is made while the target is in the fovea as opposed to parafoveally). The region of PPC we selected is also modulated by working memory load. Since longer dwell time was found in higher load conditions, it is also possible that thalamocortical connectivity is greater only when there is only one target to maintain. Behavioral and neuroimaging studies have shown that the precision of memory decreases with memory load and is highest for single item loads [124,173]. Another possibility is that, in our task, item recognition may not require a visual representation of the target item. The search display contained 5 random objects and as distractors were from different semantic categories as the target, information about the semantic category of the target is sufficient for accurate recognition of the target. Therefore, we cannot rule out that subjects were using only semantic information in their decision. Behaviorally, the benefit to search performance with search target presented visually instead of verbally is no longer evident after a 9 second delay between target presentation and search [164], suggesting that target representation in memory may be transformed from being primarily visual to some combination of visual and verbal. Therefore, our finding that target dwell time modulates thalamic

mediation of MFG-PPC connectivity might be showing greater visual representation of the target, facilitating recognition, or it might be showing that this cortico-thalamo-cortical connectivity is involved in further processing of our visual target to a form that leads to easier recognition.

Recent theories of how the network of frontal, parietal and visual regions interact propose that higher fidelity visual representation is maintained in the visual association regions rather than frontal or parietal regions [14,17,120]. Therefore, it is possible that shorter time to target (which in our task, may be a better index of visual representation) may be associated with connectivity between the prefrontal cortex, thalamus and visual regions. However, our task did not lend itself to an obvious choice of a visual region to test thalamocortical connectivity. We tried to select a lateral occipital (LOC) cluster (based on the literature showing that random objects are preferentially processed by the LOC [174–176]) from the Stimulus display (collapsed across load, as it was not present in the load contrast), and did not find behavioral modulation of the connectivity between this visual region, the MFG and the thalamus. However, as there was very widespread activation in inferior occipital and inferior temporal regions during the Stimulus display, we cannot conclude that connectivity with visual regions are not modulated by behavior. Further studies that allow better localization of a relevant visual region will be needed to better investigate the association between search behavior and thalamocortical connectivity.

Thalamocortical connectivity association during visual search

We found expected increases in both BOLD activation in the FEF, MFG, and PPC, and in cortico-thalamo-cortical connectivity between the MFG, thalamus and FEF with increased time to target at search. Longer time to target indicates a harder search task, and requires more shifts of attention (implicit or explicit), which has previously been shown to increase activation in the MFG, FEF and thalamus [76,81,138,177]. Connectivity between cortical regions has been shown to increase in search difficulty [135,136]. Our results indicate that when examining the unique effects of interaction between search efficiency with

thalamocortical connectivity and cortico-cortical connectivity, the association of cortico-thalamo-cortical connectivity with behavior is stronger. This supports the hypothesis that there is behaviorally relevant thalamic mediation of cortico-cortical connectivity during when more shifts of attention is required, and extends previous work by showing that thalamocortical connectivity is directly related to behavioral performance during search tasks in humans.

Thalamocortical connectivity for thalamic subsections

Our thalamus (prefrontal) and thalamus (parietal) seeds showed similar patterns of activity. No previous study has explicitly examined how MD and pulvinar activation differ during search, and even though neuroimaging literature has stressed the role of the pulvinar in visual search [76,81,152], the MD also shows activation during these studies. It may be that the MD and the pulvinar are difficult to separate during visual search because the task requires both visual perception and shifts of visual attention. The MD has been shown to be involved in shifts of attention and eye movements [161], while the pulvinar has been shown to be involved in perception and attention selection [20]. Both shifts of attention and attention selection are necessary during a search task, therefore to tease apart the roles of these two nuclei in visual search paradigms will require a task better designed to tease apart visual perception and shifts of attention. It is also possible that at the spatial resolution of this study (our ROIs were bordering in some regions); it is difficult to differentiate between the thalamic nuclei. Studies with improved spatial and temporal resolution, and better methods of identifying thalamic nuclei will likely be needed to tease apart differences between these two nuclei.

Conclusion

In conclusion, we found that search behavior uniquely interacts with cortico-thalamo-cortical connectivity when controlling for cortico-cortical connectivity during both the delay period and search period of a cued visual search task. We suggest that cortico-thalamo-cortical connectivity between the MFG, thalamus and FEF is important in the search process, possibly having a role in mediating shifts of attention. The MFG-thalamus-PPC connectivity appears to be involved in maintaining, or possibly transforming, memory representation in/into a form that facilitates target recognition, but not finding the target in a search task.

Chapter 5

General Discussion

The results of the studies presented in this thesis suggest that along with the documented interaction between behavior and cortico-cortical connectivity, thalamocortical also interacts with behavior in visual working memory and attention tasks.

The two studies in this thesis indicate that thalamocortical connectivity at the systems level shows task dependent modulation. We found that thalamic mediation of cortico-cortical connectivity is modulated by trial by trial changes in behavior, but shows less evidence of being modulated by rules based on stimulus category. Theories of working memory function posit that the prefrontal cortex maintains task rules along with stimulus information necessary for task completion [14,104]. If prefrontal cortex has a top-down influence on motor and visual regions in relation to task rule, it is possible that a parallel cortico-thalamocortical connection integrates rule information along with other parameters important for trial-by-trial performance of a task. Under this framework, the prefrontal cortex would send rule information to the parietal and visual association regions, and to the thalamus. The thalamus would then integrate this rule information with other sources of information, such as distracting input from memory or perception, and signals from the basal ganglia [27,29,32]. The thalamus might modulate the parietal and visual association activation based on a summation of all inputs, thereby influencing trial by trial behaviors.

The interaction between thalamocortical connectivity and behavior seen in our studies might be evidence of either information gating [74,113,114] or synchronization with cortical regions [20,25,73,116]. The thalamus functioning as a filter for irrelevant information in an information gating framework is a prominent theory of thalamic function [74,113,114]. Another theory suggests that the thalamus has a role in synchronizing brain activity among cortical regions in a task relevant manner [20,25,73,116]. A third theory of thalamic function suggests that it integrates information from multiple sources by having many neurons converge on a few thalamocortical output neurons, increasing processing speed [178]. These models are

not mutually exclusive, though with our current study designs, it is difficult to differentiate between the first two models. It is possible that thalamic integration of information is task dependent, by modulation through the reticular nucleus, which may then transfer information to cortex through synchronization [57,178]. Future studies might test if thalamocortical connectivity is more associated with information gating or synchronization by examining the effect of interference on thalamocortical connectivity.

We found little evidence supporting our hypothesis that thalamocortical connectivity influences the integrity of stimulus representation with our neural measure of representation. While electrophysiological studies indicate that the thalamus is necessary for enhancing target representation in a task dependent manner [26], it is possible that thalamocortical connectivity is not associated with higher order representations such as category information. Indeed, our results indicate that cortico-cortical connectivity may be associated with categorical representation in visual association regions. It has previously been shown that it is possible to classify individual stimuli from the pulvinar only when those stimuli are attended [77], supporting the need to examine the influence of thalamocortical connectivity in individual stimuli rather than higher order representations such as category.

The analyses we conducted to examine thalamocortical connectivity are restricted to making hypotheses of associations. Even our path analysis models used trial-by-trial betas as inputs, only allowing us to examine co-activation of different brain regions, rather than temporally direction connectivity. Directionality in our models are function of statistical regression rather than direction of neuronal information transfer. This limits our interpretation of the thalamocortical and cortico-cortical directions, as it is equally possible that the neuronal information transfer in a reverse direction from our models, or bidirectional. However, our analyses does allow us to test how behavior modulates thalamocortical connectivity in a more general manner, and were able to show that in both working memory and attention tasks, thalamocortical connectivity is associated with behavior.

A major limitation of our analyses is our inability to differentiate between the MD and Pulvinar. While we examined the thalamus (prefrontal) and thalamus (parietal) separately, our pattern of results were similar in both studies, differing only in the strength of the effect. These two nuclei are proposed to have different functions in working memory and attention, yet the resolution of our study procedures precludes us from separating their mechanisms of action.

Future studies should further investigate the relationship between thalamocortical connectivity and representation of stimuli in memory, ideally with a design that explicitly tests the precision of memory representation [124] and models neural representation better using forward encoding models [44], which our design does not allow. Future studies with improved spatial and temporal resolution and better methods of identifying thalamic nuclei will be needed to better able to tease apart differential roles of the MD and Pulvinar in working memory and attention.

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Tables

Table 3.1. Coordinates for individual right Fusiform Face Area (FFA) regions of interest

Subject	x	y	z
E1_s01	42	-42	-27
E1_s02	42	-51	-24
E1_s03	45	-51	-27
E1_s04	39	-48	-27
E1_s05	45	-45	-30
E1_s06	45	-48	-21
E1_s07	45	-54	-18
E1_s08	42	-48	-27
E1_s09	42	-48	-21
E1_s10	36	-42	-30
E1_s11	36	-45	-30
E1_s12	45	-42	-27
E2_s01	39	-52	-14
E2_s02	39	-43	-20
E2_s03	42	-49	-17
E2_s04	42	-58	-20
E2_s05	42	-52	-20
E2_s06	48	-49	-26
E2_s07	45	-55	-20
E2_s08	36	-40	-23
E2_s09	36	-46	-17
E2_s10	45	-49	-26
E2_s11	48	-52	-23
E2_s12	42	-46	-23
E2_s13	39	-46	-20
E2_s14	45	-43	-14
E2_s15	39	-49	-14
E2_s16	39	-43	-23
E2_s17	45	-49	-26
E2_s18	36	-46	-20
E2_s19	42	-49	-17
E2_s20	36	-55	-17
E2_s21	39	-46	-23

Table 3.2. Coordinates for individual right Parahippocampal Place Area (PPA) regions of interest

Subject	x	y	z
E1_s01	27	-45	-15
E1_s02	30	-45	-12
E1_s03	27	-48	-12
E1_s04	30	-45	-18
E1_s05	30	-42	-12
E1_s06	21	-45	-9
E1_s07	30	-51	-15
E1_s08	27	-42	-15
E1_s09	30	-45	-9
E1_s10	30	-42	-9
E1_s11	27	-45	-6
E1_s12	36	-45	-12
E2_s01	30	-43	-8
E2_s02	33	-40	-8
E2_s03	27	-46	-8
E2_s04	21	-37	-11
E2_s05	27	-37	-17
E2_s06	33	-40	-8
E2_s07	24	-49	-11
E2_s08	33	-49	-8
E2_s09	27	-52	-8
E2_s10	27	-46	-8
E2_s11	27	-49	-8
E2_s12	30	-46	-8
E2_s13	24	-43	-8
E2_s14	33	-40	-11
E2_s15	24	-40	-8
E2_s16	24	-43	-8
E2_s17	24	-37	-14
E2_s18	30	-43	-8
E2_s19	33	-43	-8
E2_s20	24	-55	-5
E2_s21	27	-40	-11

Table 3.3. Coordinates for individual left Middle Frontal Gyrus (MFG) regions of interest

Subject	x	y	z
E1_s01	-45	8	37
E1_s02	-42	8	40
E1_s03	-45	5	49
E1_s04	-39	8	49
E1_s05	N/A	N/A	N/A
E1_s06	-42	-1	34
E1_s07	N/A	N/A	N/A
E1_s08	-42	11	49
E1_s09	-42	-1	43
E1_s10	N/A	N/A	N/A
E1_s11	-42	11	49
E1_s12	-45	11	34
E2_s01	-51	20	22
E2_s02	-57	20	25
E2_s03	-54	26	25
E2_s04	-54	26	22
E2_s05	-39	23	25
E2_s06	N/A	N/A	N/A
E2_s07	-48	23	22
E2_s08	-54	26	25
E2_s09	N/A	N/A	N/A
E2_s10	-51	17	19
E2_s11	-45	17	22
E2_s12	-48	17	31
E2_s13	-36	11	28
E2_s14	-48	23	22
E2_s15	-45	26	25
E2_s16	-39	23	22
E2_s17	-51	23	28
E2_s18	-51	26	34
E2_s19	-48	14	31
E2_s20	-48	26	25
E2_s21	-48	17	28

Table 4.1. Behavioral results for search performance measures for 1-Target and 2-Target conditions

Behavioral Measure	1-Target condition	2-Target condition
Reaction Time	1096±245	1379±244
Time to Target	434±81	617±104
Target Dwell Time	672±222	762±199
Initial Saccade Latency	273±38	292±53
Initial Saccade Direction	0.55±0.23	0.53±0.16
Target Saliency	-0.0127±0.008	-0.0083±0.008

Table 4.2. Load dependent activity at Stimulus, Delay and Search. Superior parietal lobule, SPL; inferior parietal lobule, IPL; intraparietal sulcus, IPS; dorsal anterior cingulate cortex, dACC; pre-supplementary motor area, pre-SMA; middle frontal gyrus, MFG; superior frontal sulcus, SFS; anterior insula, aI; Inferior occipital cortex/Inferior temporal cortex, Inf Occip/IT

Region	x	y	z	z-score	Cluster size
<i>Significant load dependent activity at Stimulus</i>					
L SPL	-33	-57	48	5.87	1792
L IPS	-21	-60	33	5.27	
L IPL	-33	-45	39	4.90	
R IPL	30	-57	36	4.88	
R SPL	36	-57	45	4.69	
L Inf Occip/IT	-33	-48	-18	5.51	783
pre-SMA	0	15	45	5.22	858
L aI	-48	15	-6	4.99	567
L MFG	-39	6	30	4.58	
L FEF	-36	-3	48	4.45	
L SFS	-30	48	30	4.18	148
R aI	24	18	0	5.91	224
R MFG	48	12	24	4.46	93
R SFS	36	51	18	4.57	158
<i>Significant load dependent activity at Delay</i>					
R IPL*	33	-48	42	4.76	25
pre-SMA	0	27	42	4.10	34
R aI	36	21	-3	4.24	31
L aI	-33	21	-3	3.95	22
<i>Significant load dependent activity at Search</i>					
L IPS	-27	-72	33	3.94	163
R IPS	30	-66	33	4.24	226
L MFG	-42	9	27	4.22	89
R MFG	51	18	27	3.62	27
pre-SMA	-3	18	45	4.26	179
L aI	-30	18	-6	4.86	111
R aI	27	21	0	4.40	152
L Fusiform	-42	-54	-5	3.95	107
R Fusiform	33	-33	-24	4.52	30

Table 4.3. Significant clusters associated with search performance measures. Superior parietal lobule, SPL; intraparietal sulcus, IPS; dorsal anterior cingulate cortex, dACC; pre-supplementary motor area, pre-SMA; middle frontal gyrus, MFG; anterior insula, aI

Region	x	y	z	z-score	Cluster size
<i>Reaction Time at search: positive association (greater activation correlated with longer Reaction Time)</i>					
R SPL	30	-60	48	5.33	119
R IPS	33	-60	36	4.27	
L IPS	-30	-75	24	4.38	185
L SPL	-33	-57	48	4.21	
dACC	9	30	18	4.65	165
pre-SMA	-3	18	42	4.44	
R MFG	36	18	21	3.85	23
L MFG	-45	18	21	4.51	109
R aI	36	21	-3	4.29	119
L aI	-33	24	-3	4.80	102
<i>Time to Target at search: positive association (greater activation correlated with longer Time to Target)</i>					
R IPS	18	-75	42	4.19	83
R IPL	30	-60	42	3.99	
L IPS	-21	-72	39	3.94	87
L IPL	-27	-54	48	3.85	
dACC	-33	24	33	4.05	42
L MFG	-30	6	24	4.02	26
R aI	36	24	-3	3.80	37
L aI	-33	24	-3	4.18	44

Table 4.4. Individual path coefficients of path models tested at Delay and Search

Path	Path coefficient	Significance
<i>Path model between MFG, thalamus (prefrontal) and PPC at delay</i>		
MFG→PPC	0.318	p<0.001
MFG→Thalamus (prefrontal)	0.457	p<0.001
Thalamus (prefrontal)→PPC	0.200	p<0.001
<i>Path model between MFG, thalamus (parietal) and PPC at delay</i>		
MFG→PPC	0.336	p<0.001
MFG→Thalamus (parietal)	0.405	p<0.001
Thalamus (parietal)→PPC	0.178	p<0.001
<i>Path model between MFG, thalamus (prefrontal) and FEF at search</i>		
MFG→FEF	0.308	p<0.001
MFG→Thalamus (prefrontal)	0.438	p<0.001
Thalamus (prefrontal)→FEF	0.200	p<0.001
<i>Path model between MFG, thalamus (parietal) and FEF at search</i>		
MFG→FEF	0.318	p<0.001
MFG→Thalamus (parietal)	0.437	p<0.001
Thalamus (parietal)→FEF	0.180	p<0.001

Figures

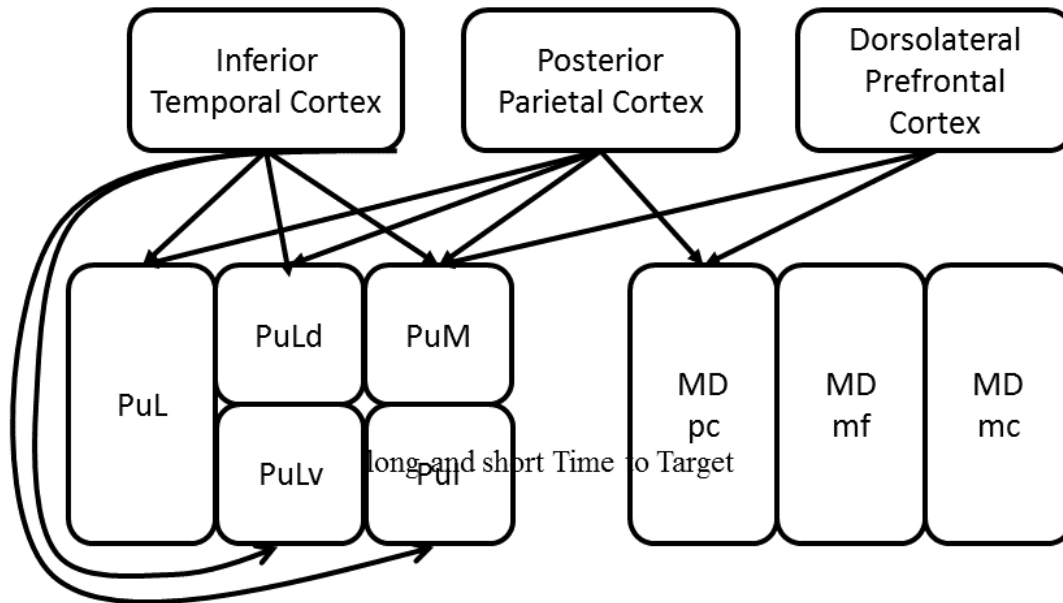


Figure 2.1. Schematic of neuroanatomical connectivity between temporal, parietal and prefrontal cortex and the pulvinar and mediodorsal nucleus of the thalamus. Thalamic subdivisions shown are the lateral pulvinar (PuL), dorsoal portion (PuLd), ventral portion (PuLv), medial pulvinar (PuM), inferior pulvinar (PuI), mediodorsal thalamus (MD), parvocellular portion (MDpc), magnocellular portion (MDmc) and pars multiforms (MDmf). (Based on Romanski et al. 1997; Ray and Price 1993; Baleyrier and Morel 1992; Selemon and Goldman-Rakic 1988; Goldman-Rakic and Porrino 1985)

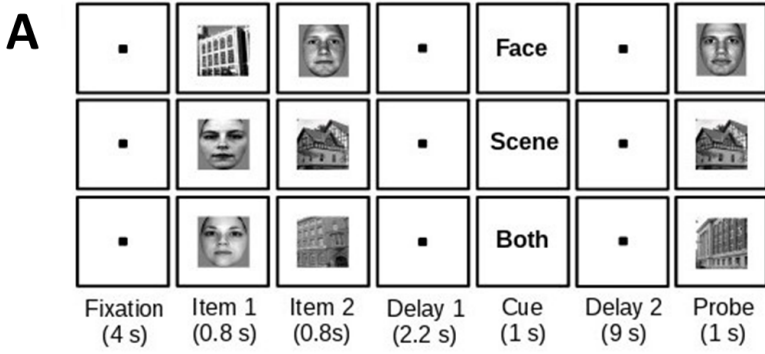
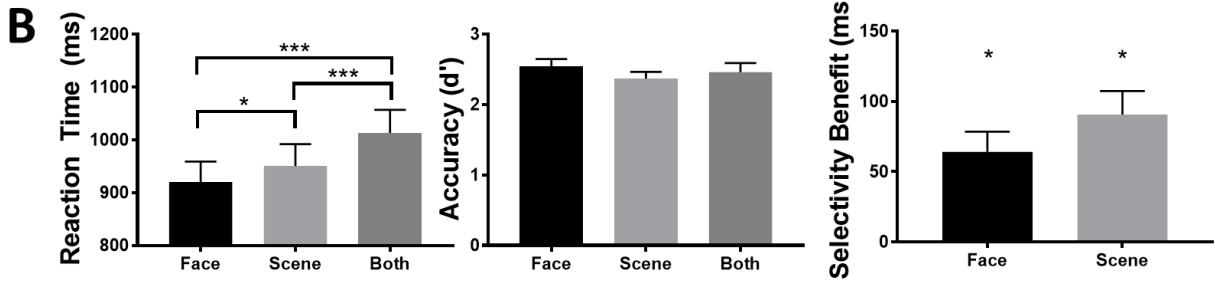


Figure 3.1. A. Schematic of events in the task condition. For each trial, two stimuli were presented, one scene image and one face image. After a short delay, participants were cued to Remember Face, Remember Scene or Remember both images. Memory accuracy was probed with a image of the same category as cued. Figure reproduced with permission from Le et al., (under review). **B.** Summary of reaction time, accuracy (d') for Face, Scene and Both conditions and Selectivity Benefit for Face and Scene.



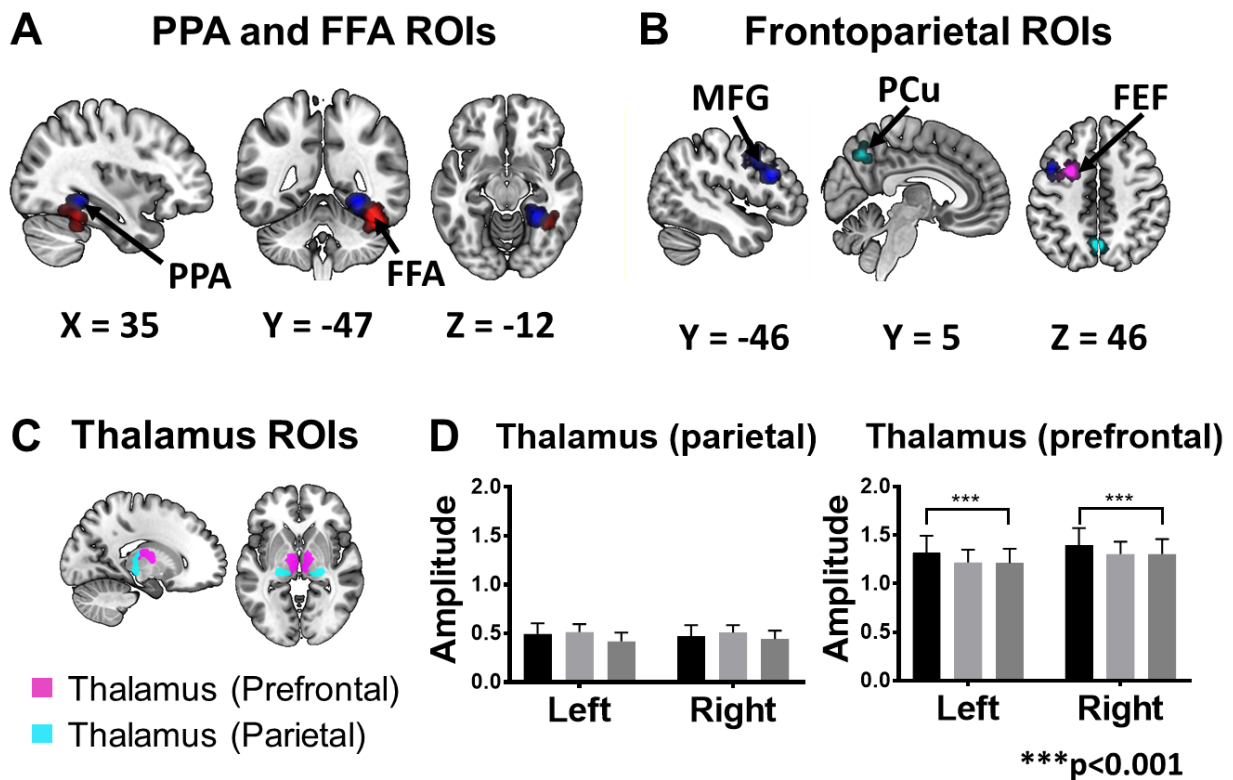


Figure 3.2. **A.** Red: Fusiform face area (FFA) and Blue: parahippocampal place area (PPA) regions of interest (ROIs) based on localizer task **B.** Frontoparietal ROIs based on Non Select > Select comparison at delay. **C.** ROIs based on DTI connectivity to the prefrontal cortex and parietal cortex (Behrens et al., 2003). **D.** Thalamus (parietal) and thalamus (prefrontal) amplitude differences between the Face, Scene and Both conditions during the post-cue delay period.

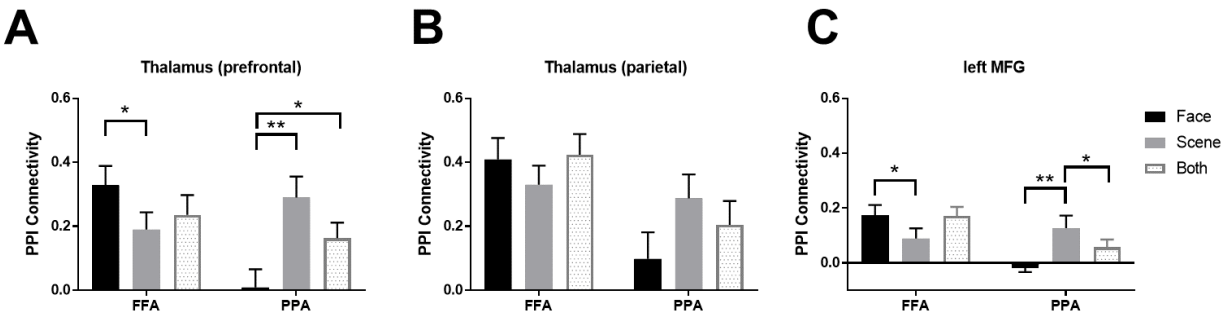
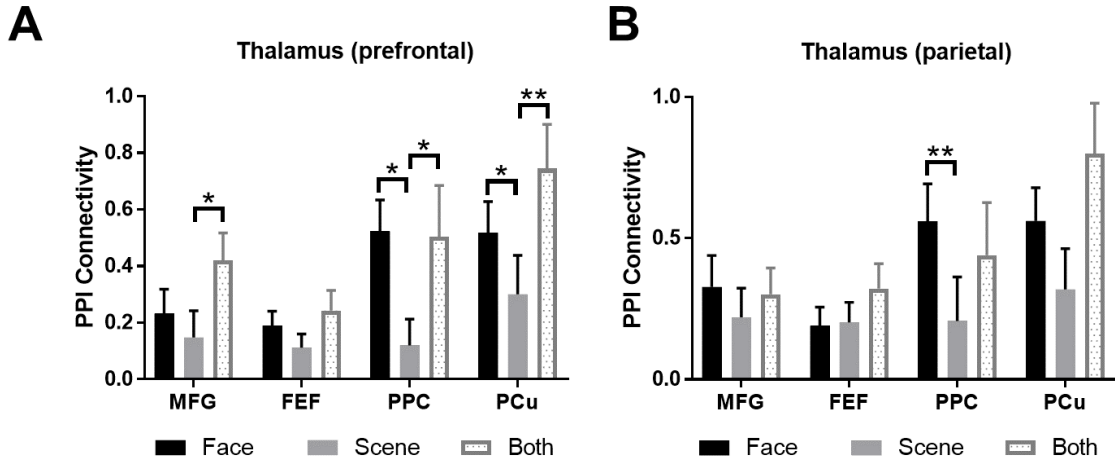


Figure 3.3 A. Connectivity from the thalamus (prefrontal) to both the Fusiform Face Area (FFA) and Parahippocampal Place Area (PPA) showed significant difference between conditions ($F(2,64)=3.15$, $p<0.05$ and $F(2,64)=6.45$, $p<0.01$ respectively). **B.** Connectivity from the thalamus (parietal) the FFA and PPA showed no significant difference between conditions ($F(2,64)=0.98$, $p=0.380$ and $F(2,64)=1.81$, $p=0.173$ respectively). **C.** Connectivity between the left middle frontal gyrus (MFG) and the FFA showed a trend towards significance between conditions ($F(2,64)=2.43$, $p=0.096$) and a significant difference between conditions with the PPA ($F(2,64)=3.73$, $p<0.05$). Significance presented as * $p<0.05$, ** $p<0.01$



*p<0.05, **p<0.01

Figure 3.4. A. Connectivity between the left thalamus (prefrontal) and the left middle frontal gyrus (MFG), frontal eye fields (FEF), posterior parietal cortex (PPC) and Precuneus (PCu). The PPC and PCu showed significant differences between conditions ($F(2,40)=3.753$, $p<0.05$ and $F(2,40)=6.515$, $p<0.01$ respectively), no other frontoparietal region shows significant difference between conditions (F 's<2, p 's>0.1). **B.** Connectivity between the left thalamus (parietal) and the left MFG, FEF, PPC and PCu. The PCu shows a trend towards a significance between conditions ($F(2,40)=2.94$, $p=0.053$), no other frontoparietal region shows significant difference between conditions (F 's<2, p 's>0.1).

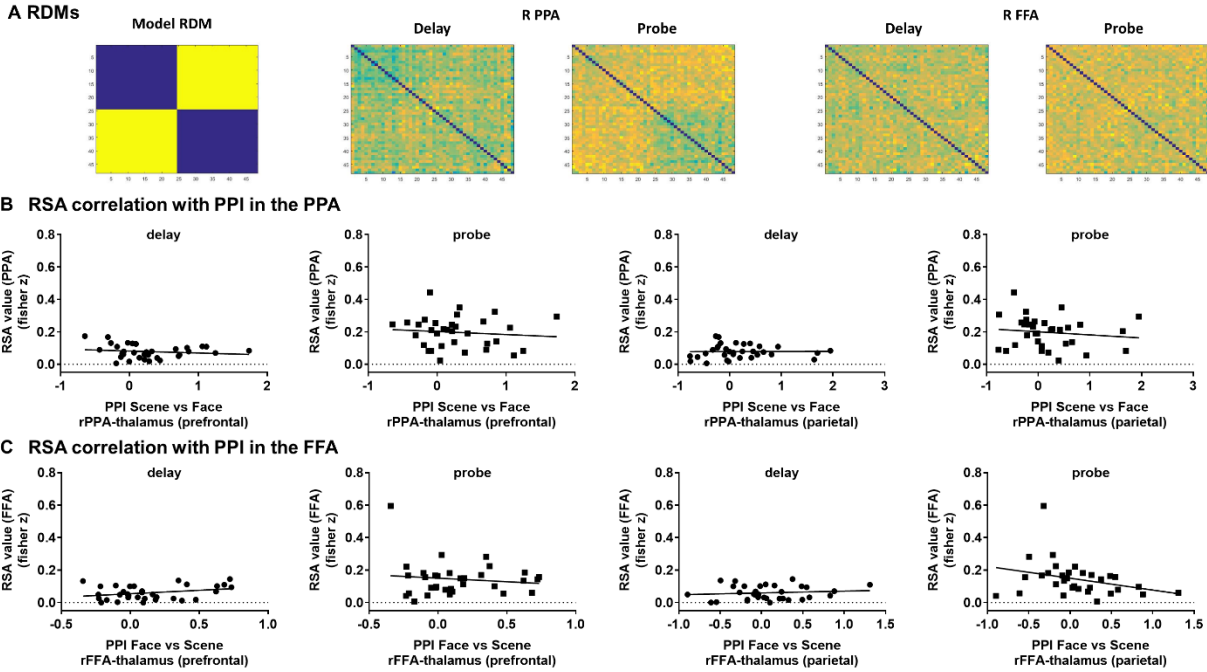


Figure 3.5. **A.** Average Representational Dissimilarity Matrices (RDM) for the parahippocampal place area (PPA) and fusiform face area (FFA) at delay and probe period of the trial. **B.** Correlation psychophysiological interactions (PPI) between the thalamus and PPA and between representational similarity area (RSA) delay and probe. **C.** PPI between the thalamus and PPA and between RSA at delay and probe.

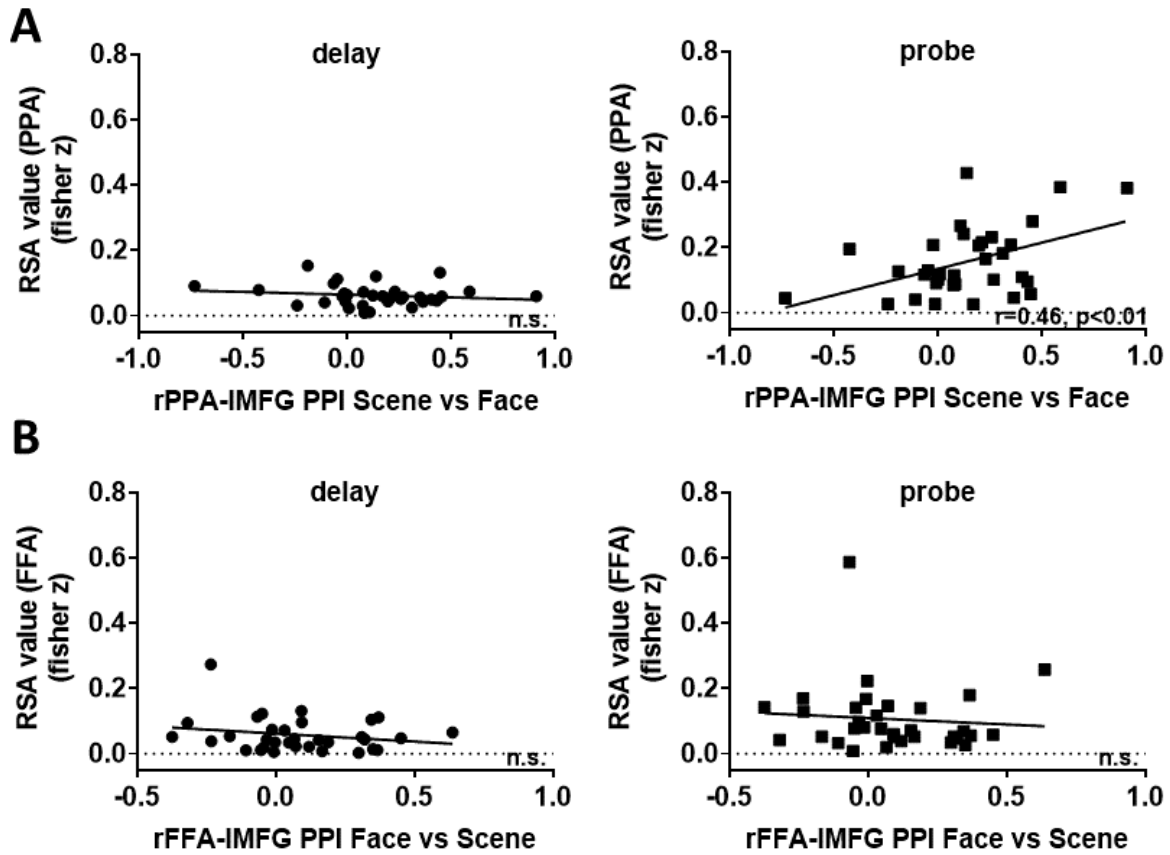


Figure 3.6. **A.** Correlation of psychophysiological interactions (PPI) between the left MFG and PPA in the Scene>Face contrast with representational similarity area (RSA) during the delay and probe **B.** Correlation of PPI between the left MFG and FFA in the Face>Scene contrast RSA during the delay and probe.

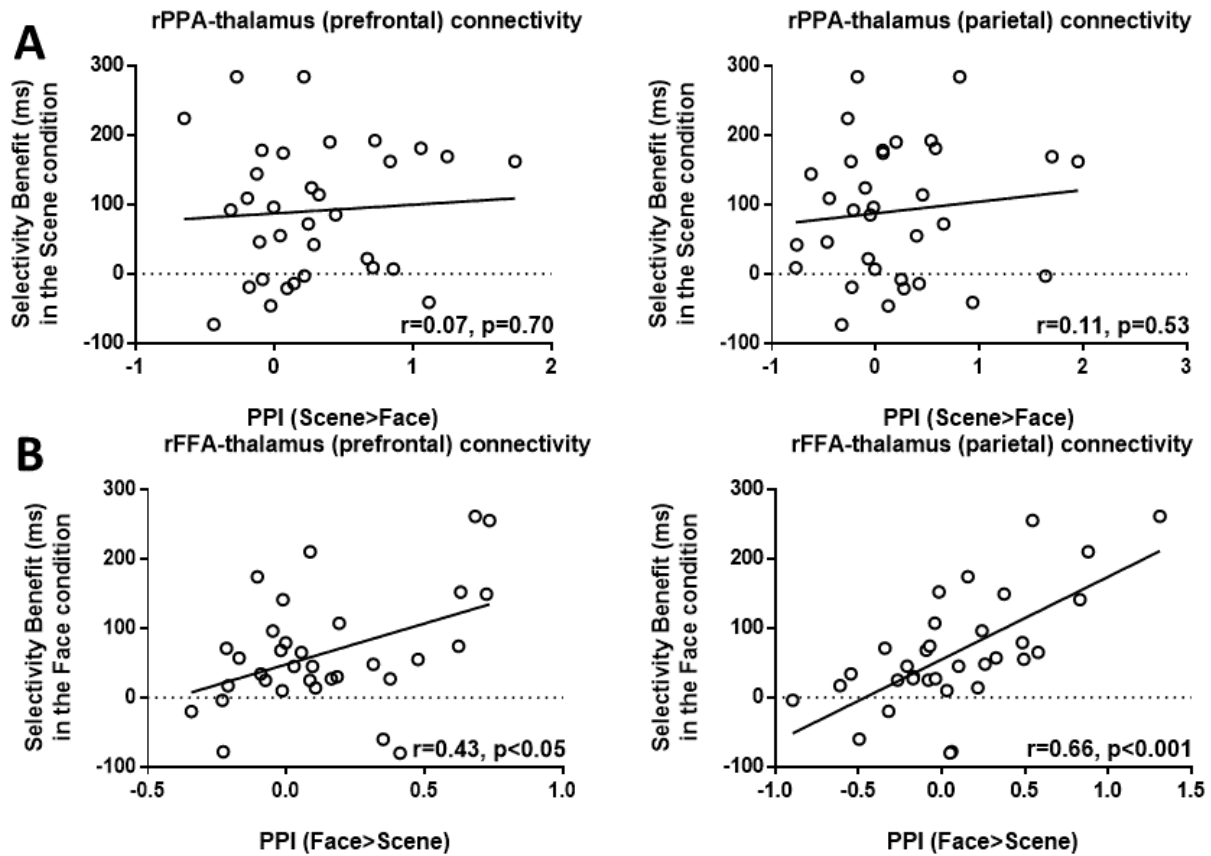


Figure 3.7. Correlation between psychophysiological interaction (PPI) between **A.** thalamus (prefrontal and parietal) and the behavioral advantage seen when selectively remembering only a scene stimulus compared to remembering both scene and face stimuli (Selectivity Benefit in the Scene condition) and **B.** thalamus (prefrontal and parietal) and Selectivity Benefit in the Face condition.

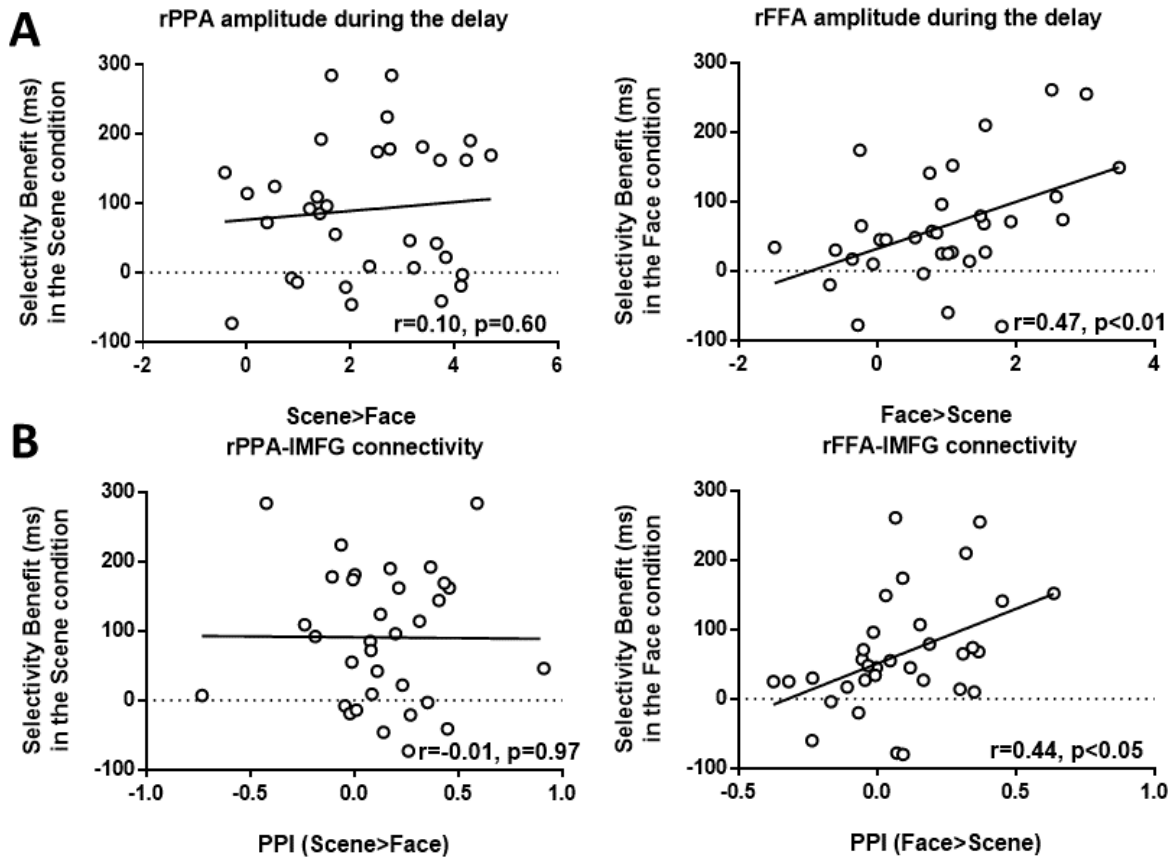


Figure 3.8. Correlation cortical activity and connectivity with Selectivity Benefit **A.** PPA and FFA amplitude association with Selectivity Benefit in the Scene and Face conditions respectively **B.** MFG-PPA and MFG-FFA connectivity association with Selectivity Benefit in the Scene and Face conditions respectively.

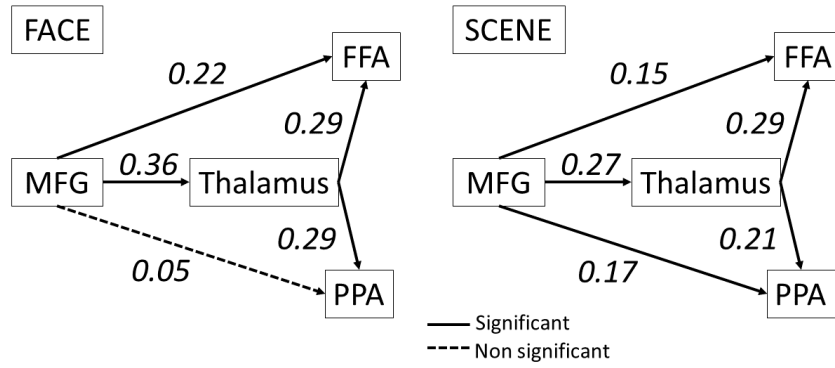


Figure 3.9. Path model constructed to investigate cortico-thalamo-cortical and cortico-cortical connectivity between MFG, thalamus, FFA and PPA during Face and Scene conditions.

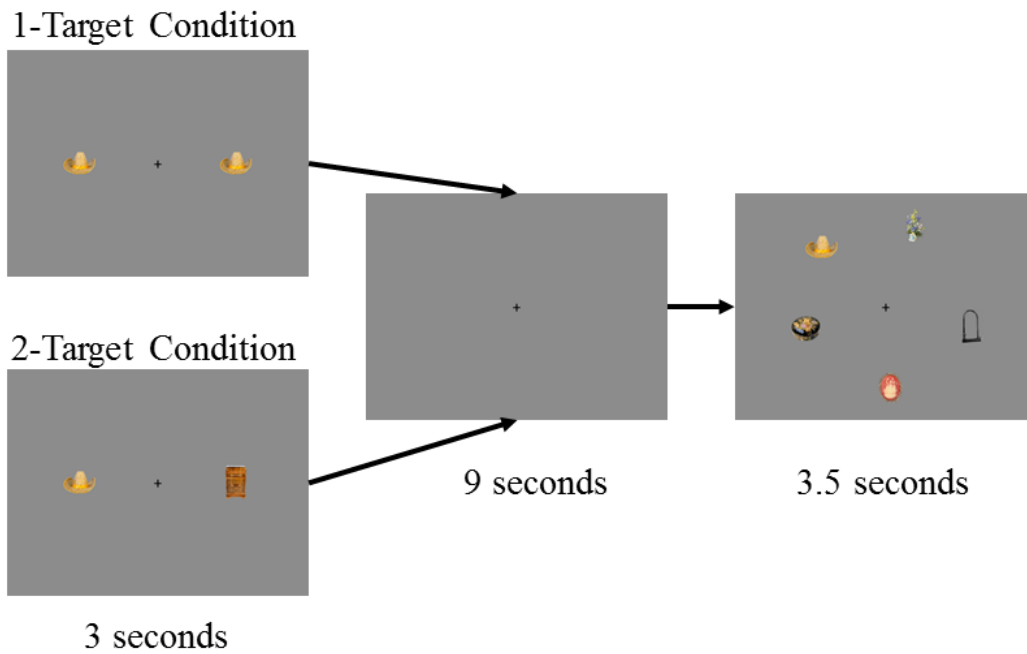


Figure 4.1. A schematic showing events in a trial. Each trial began with a 3 second preview of the targets searched for followed by a 9 second delay. The search display was presented for 3.5 seconds. Participants were instructed to respond by pressing a button while looking at the target.

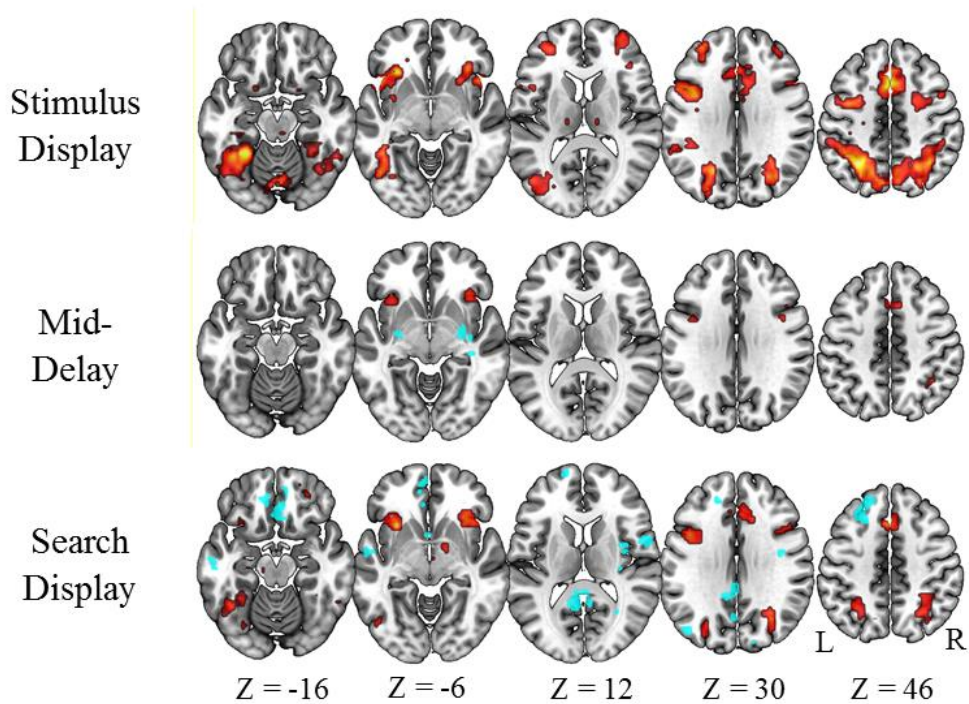


Figure 4.2. Activation associated with load during the stimulus display, at mid-delay and during the search display. Hot colors show greater activation in 2-Target > 1-Target contrast, cool colors show greater activation in 1-Target > 2-Target contrast. Images threshold at $p < 0.001$, $k = 0$.

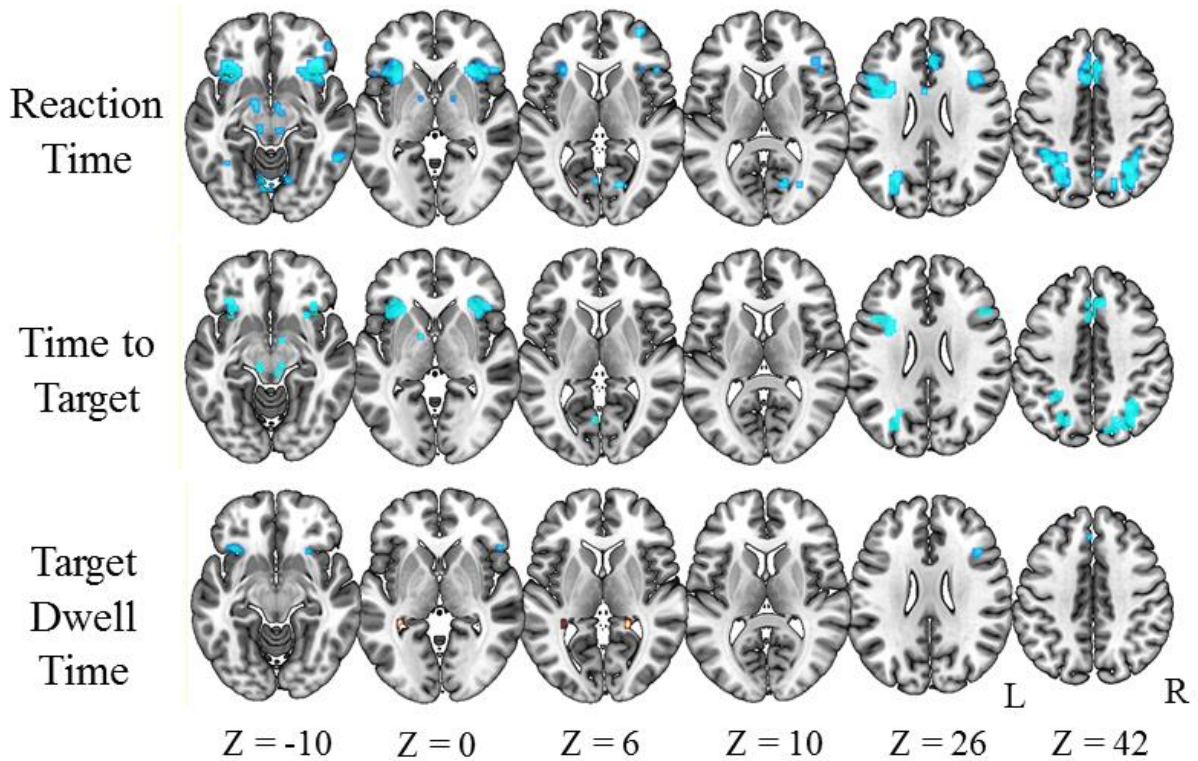


Figure 4.3. Parametric modulation of search period activity by search performance measures Reaction Time, Time to Target and Target Dwell Time masked by load related activation (threshold at $p < 0.05$) to show only regions associated with working memory load. Hot colors show regions that are correlated with better search, cool colors show regions that are associated with worse search. Images threshold at $p < 0.001$, $k = 0$.

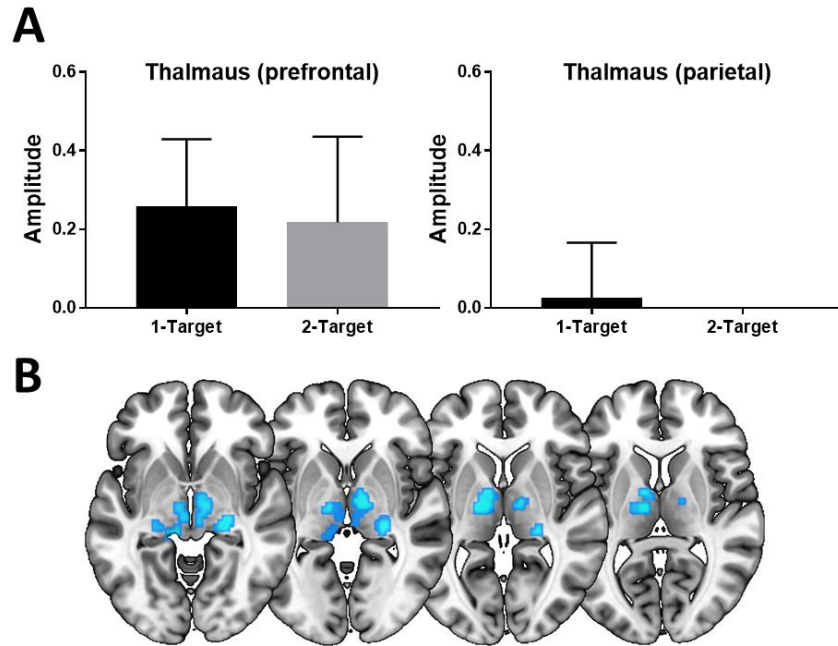
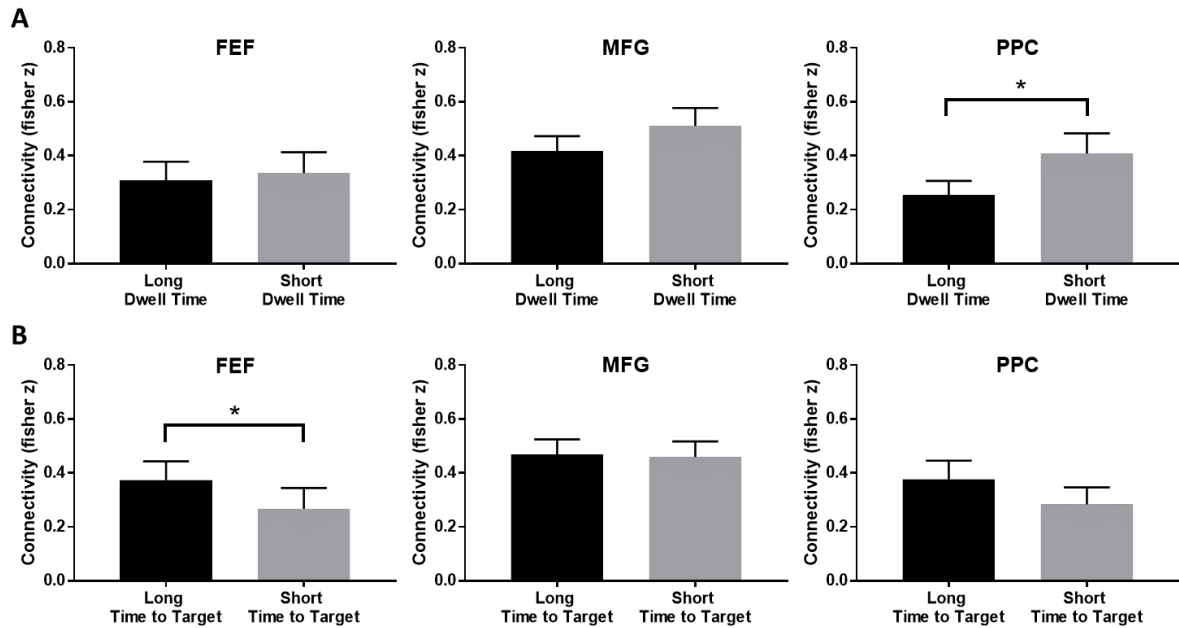


Figure 4.4. **A.** Amplitude difference for 1-Target and 2-Target conditions for the thalamus (prefrontal) and thalamus (parietal) amplitude at Delay. **B.** Clusters within the thalamus that are significantly associated with longer reaction time at Search



*p<0.05

Figure 4.5. Beta series correlations at Delay between the thalamus (prefrontal) and the frontal eye fields (FEF), middle frontal gyrus (MFG) and posterior parietal cortex (PPPC) for trials sorted by long and short (median split) Time to Target and Dwell Time

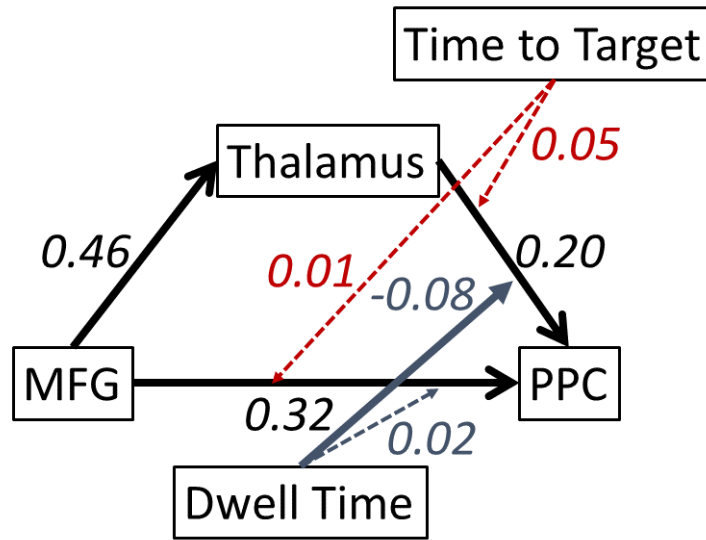


Figure 4.6. Path model testing the Time to Target and Dwell Time modulation of MFG → PPC and MFG → Thalamus (prefrontal) → PPC connectivity at Delay

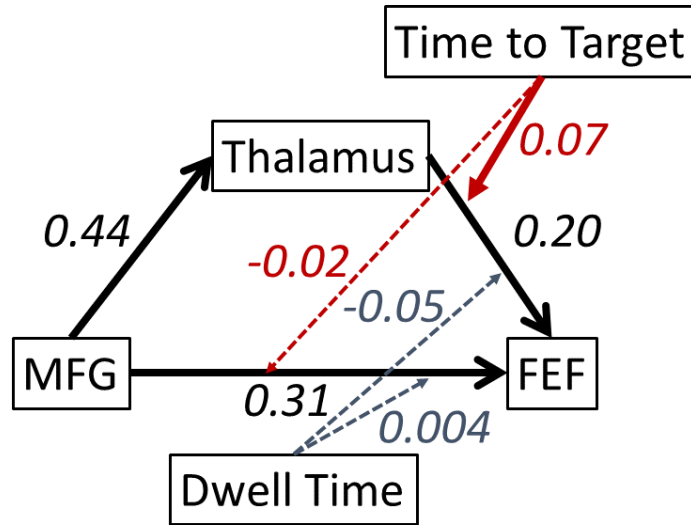


Figure 4.7. Path model testing the Time to Target and Dwell Time modulation of MFG → FEF and MFG → Thalamus (prefrontal) → FEF connectivity at Search