

Electronic Thesis and Dissertation Repository

7-4-2014 12:00 AM

Revisiting working memory: Are domain, process and global models mutually exclusive, nested or orthogonal?

Jeffrey P. Wong
The University of Western Ontario

Supervisor
Dr. Adrian Owen
The University of Western Ontario

Graduate Program in Neuroscience
A thesis submitted in partial fulfillment of the requirements for the degree in Master of Science
© Jeffrey P. Wong 2014

Follow this and additional works at: <https://ir.lib.uwo.ca/etd>



Part of the [Cognitive Neuroscience Commons](#), and the [Systems Neuroscience Commons](#)

Recommended Citation

Wong, Jeffrey P., "Revisiting working memory: Are domain, process and global models mutually exclusive, nested or orthogonal?" (2014). *Electronic Thesis and Dissertation Repository*. 2181.
<https://ir.lib.uwo.ca/etd/2181>

This Dissertation/Thesis is brought to you for free and open access by Scholarship@Western. It has been accepted for inclusion in Electronic Thesis and Dissertation Repository by an authorized administrator of Scholarship@Western. For more information, please contact wlsadmin@uwo.ca.

REVISITING WORKING MEMORY: ARE DOMAIN, PROCESS, AND GLOBAL
MODELS MUTUALLY EXCLUSIVE, NESTED OR ORTHOGONAL?

A revised model of neural mechanisms underlying working memory

(Thesis format: Monograph)

by

Jeffrey Wong

Graduate Program in Neuroscience

A thesis submitted in partial fulfillment
of the requirements for the degree of
Master of Science

The School of Graduate and Postdoctoral Studies
The University of Western Ontario
London, Ontario, Canada

© Jeffrey Penn Wong 2014

By
Jeffrey Penn Wong
Master of Science
Department of Neuroscience
Western University Canada
2014

Working memory (WM) is a cognitive function whereby task-relevant information is actively maintained and manipulated in mind for goal-directed behaviour. Three competing models, here dubbed the global, domain and process models, have attempted to explain its neural underpinnings. Despite extensive research however, no consensus has been reached. Here, we use two new WM paradigms to demonstrate that all three models are partially correct. In the first experiment, our results show that selected frontoparietal regions (MD), from the global model, are largely stimulus-independent. However, more posterior and caudal frontoparietal regions show stimulus-dependent activations as described by the domain model. In the second experiment, our results reveal that a dorsal MD sub-network is more active when information is manipulated, as described by the process model. Thus, WM is best represented by all three models, with the process model nested within the global, and the domain model partially independent from the others.

Keywords

Key Words: Working Memory, Frontoparietal Cortex, Cognitive functions, Domain model, Process model, Adaptive coding, Multiple Demand, fMRI, Independent Components Analysis

Acknowledgments

Many people have defined my graduate experience and without their support, this achievement would not have been possible. I would like to show my appreciation to Dr. Adrian Owen for directing me throughout the entire process of my degree giving critical feedback about my thesis and life decisions. Likewise, I would like to take the time to express my utmost gratitude to Dr. Adam Hampshire for his invaluable guidance and intellectual proficiency. I also offer my appreciation to Mr. Adam McLean for patiently helping me scan participants in the MRI late at night. Lastly, I would like to thank all members of the Neuroscience graduate programme and Brain and Mind institute for giving me such an amazing and heartfelt experience during my graduate career.

Table of Contents

Acknowledgments.....	iii
Table of Contents.....	iv
List of Tables.....	vi
List of Figures.....	vii
List of Abbreviations.....	viii
1.1 Introduction to Working Memory.....	1
1.2 Experiment 1 - Task design.....	5
1.3 Experiment 2 - Task design.....	7
1.4 Participants.....	9
1.5 Data acquisition.....	10
1.6 Independent Components Analysis.....	11
1.7 Fixed and Random Effects Analyses.....	12
1.8 Experiment 1: Behavioural Results.....	13
1.9 Experiment 1: Neuroimaging Results.....	15
1.10 Experiment 1: ROI results.....	16
1.11 Experiment 1: Whole brain analyses.....	21
1.12 Experiment 2: Behavioural Results.....	26
1.13 Experiment 2: Neuroimaging Results.....	28
1.14 Experiment 2: ROI results.....	30
1.15 Experiment 2: Whole brain analyses.....	34
1.16 Discussion.....	37
1.17 Independent buffers outside of MD.....	38
1.18 Adaptive coding and specialisation.....	40
1.19 Recent Meta-analysis.....	42

1.20 Conclusion.....	43
References or Bibliography	44

List of Tables

Table 1: Correlation Matrix of Accuracy Results	20
Table 2: Peak activation coordinates from whole brain analysis of experiment 1.	24
Table 3: Peak activation coordinates from whole brain analysis of experiment 2	36

List of Figures

Figure 1: Extracted networks from MD	3
Figure 2: Task design of experiment 1.	6
Figure 3: Task design of experiment 2.	8
Figure 4: Behavioural results from experiment 1	14
Figure 5: Extracted ICA components from experiment 1.....	15
Figure 6: ROI analyses during encoding period of experiment 1	17
Figure 7: ROI analyses during the delay period of experiment 1	18
Figure 8: Accuracy-matched contrasts within the ventral network	20
Figure 9: Whole-brain analyses of stimulus-specific activations.	22
Figure 10: Baseline activation during the encoding period of trials separated by domain.....	23
Figure 11: Baseline activation during the delay period of trials separated by domain.....	23
Figure 12: Whole-brain analysis of load-specific activations during encoding.	25
Figure 13: Behavioural results from experiment 2	27
Figure 14: Extracted ICA components from experiment 2.....	28
Figure 15: Overlapped components from both experiments.....	29
Figure 16: ROI analyses during the encoding period of experiment 2	31
Figure 17: Significant interacting effects during the delay period of experiment 2	33
Figure 18: Whole-brain analyses from experiment 2.	35
Figure 19: Whole-brain analysis of high versus low load manipulation trials	35

List of Abbreviations

WM	Working Memory
MD	Multiple Demand
fMRI	Functional Magnetic Resonance Imaging
BOLD	Blood-Oxygen-Level-Dependent
IFS	Inferior Frontal Sulcus
AI/FO	Anterior Insula / Frontal Operculum
IPS	Intraparietal Sulcus
SMA/ACC	pre-Supplementary Motor Area / Anterior Cingulate Cortex
LPFC	Lateral Prefrontal Cortex
DLPFC	Dorsolateral Prefrontal Cortex
VLPFC	Ventrolateral Prefrontal Cortex
ICA	Independent Components Analysis
ROI	Region of Interest
FDR	False Discovery Rate
RT	Reaction Time

1.1 Introduction to Working Memory

Working memory (WM) refers to the set of cognitive control functions that allow task-relevant information to be temporarily maintained and processed in the brain during goal-directed behaviour (Baddeley & Hitch, 1974). Intact WM is a prerequisite for reasoning, comprehension, planning and fluid intelligence. Many psychiatric and neurological disorders including schizophrenia, attention deficit/hyperactivity disorder and Alzheimer's have been associated with impairments in WM (Baddeley, 1986; Jonides, 1995). Thus, studying the neural correlates of WM can help us better understand cognitive dysfunction in clinical populations. Three models, here dubbed the global (Duncan, 2001), domain (Levy & Goldman-Rakic, 2000) and process (Petrides, 1994) models, have attempted to explain the neural underpinnings of WM. However, despite decades of research, no consensus regarding the functional brain organisation of WM has ever been reached. In part, this is due to poorly controlled visual display and motor response confounds. Furthermore, although there is substantial evidence promoting each perspective, all three models are generally treated as mutually exclusive to one another. In this study, we propose that all three models are partially correct as they either describe the neural-anatomical correlates of WM at different levels of detail or assign particular components of WM to different brain regions.

The global model proposes that selected frontoparietal brain regions with adaptive coding properties are recruited during a broad range of cognitive functions including WM. These brain regions include the inferior frontal sulcus (IFS), anterior insula/frontal operculum (AI/FO), bilateral intraparietal sulcus (IPS) and pre-supplementary motor area/anterior cingulate cortex (SMA/ACC) (Duncan, 2006). Neuronal populations within these regions rapidly adapt to code for task-relevant information including target stimuli, responses and rules (Duncan, 2001; Miller & Cohen, 2001). In fact, the same brain areas have been activated by many other psychological tasks including perceptual and target interference tasks (Duncan, 2006; Duncan & Owen, 2000). As such, it has been dubbed the Multiple Demand (MD) cortex for its contributions to multiple cognitive processes. Activations within these areas have also been demonstrated to correlate with individual differences in IQ scores (Gray *et al.*, 2003). Furthermore, volume of brain damage within

but not outside of these regions has been shown to correlate with drops in IQ scores following brain injury (Woolgar *et al.*, 2010). Consequently, the global model postulates that WM, attention and cognitive control are facets of the same general neural system (Duncan, 2006). Unlike the domain and process models, the global model describes a system that is not specialised for any particular stimulus domain or cognitive process but instead, rapidly adapts to code for whatever task is currently at hand.

In sharp contrast, the domain model proposes that the lateral prefrontal cortex (LPFC) sub-regions process specific categories of information. More specifically, this stimulus-dependent model argues that the ventrolateral prefrontal cortex (VLPFC) processes non-spatial information whereas the dorsolateral prefrontal cortex (DLPFC) processes spatial information (Levy & Goldman-Rakic., 2000). In line with this view, it has been reported that the VLPFC is active when objects are being maintained in WM (Courtney *et al.*, 1997), whilst the caudal superior frontal gyrus is active when spatial information is maintained (Courtney *et al.*, 1998). Furthermore, a number of studies have demonstrated that Broca's area (left BA 44/45) is crucial for sub-vocal rehearsal and verbal WM (Cohen *et al.*, 1997; Awh *et al.*, 1996). Thus the domain model postulates that the LPFC sub-regions process specific stimulus domains in an extension of the ventral-dorsal subdivision of the primary visual cortex (Ungerleider & Haxby, 1994).

The process model proposes that the VLPFC and DLPFC functionally dissociate based on the type of cognitive processes that they support as opposed to the specific stimulus domain that they manage. More specifically, this stimulus-independent model argues that the VLPFC supports simple processes including active maintenance and selective attention, whereas the DLPFC supports higher order processes including the monitoring and manipulation of maintained information (Petrides, 1994; Owen *et al.*, 1998). In support of this view, primates with mid-DLPFC lesions were reported to perform normally on recognition-based memory tasks (Petrides, 1991) but were impaired on self-ordered search tasks (Petrides, 1995). Furthermore, human neuroimaging evidence has demonstrated that spatial tasks with simple maintenance requirements recruit the VLPFC whereas the reorganisation of verbal information recruits the DLPFC (Owen *et al.*, 1996). Moreover, when the same cognitive tasks are performed using different

stimulus domains, the same brain regions are recruited (Owen *et al.*, 1998). Therefore, the process model postulates that the LPFC functionally dissociates based on the type of cognitive process that is applied as opposed to the domain of information that is being processed.

There is substantial evidence for all three perspectives of the functional organisation of WM but no consensus has been reached as the models are usually viewed as mutually exclusive. However, a recent study demonstrated that a ventral-dorsal functional axis similar to the process model can be found *within* the MD regions of the global model (Hampshire *et al.*, 2012). Specifically, the authors used factor analyses on neuroimaging data from twelve different cognitive tasks. The results revealed that whilst all MD regions were recruited by all tasks, there were two functionally dissociable and spatially distinct MD sub-networks (Figure 1). Tasks that required short-term memory maintenance most strongly activated the ventral network whilst tasks that required reasoning or planning processes most strongly activated the dorsal network. Thus, the process model may in fact be nested *within* the anatomical regions posited by the global model. Interestingly, a third network was also identified that was most strongly activated to tasks with verbal stimuli. The authors proposed that a spatial equivalent of the new component could also exist within the frontal lobes but in regions outside of MD areas. For all of these reasons, the domain, process and global models may not be mutually exclusive.

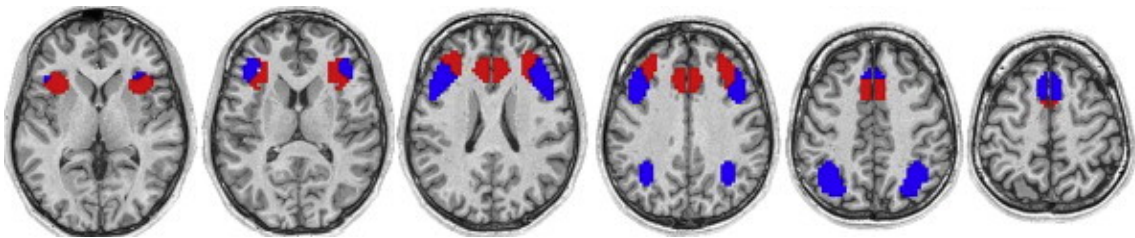


Figure 1: Extracted networks from MD (Hampshire *et al.*, 2012). The ventral network (red) recruited the AI/FO, superior frontal sulcus and ventral portion of the SMA/ACC whilst the dorsal network (blue) recruited the IFS, IPS and dorsal portion of the SMA/ACC.

Here, we use functional magnetic resonance imaging (fMRI) and two novel WM tasks to determine whether evidence for all three models could be derived from within the same task context. Firstly, we applied an independent component analysis (ICA) to the neuroimaging data of both WM tasks in order to replicate the previous findings of the ventral and dorsal MD sub-networks. Then we determined whether MD functional networks or regions outside of MD cortex responded specifically to different stimulus domains. Finally, we examined whether the MD functional networks were sensitive to the type of cognitive processes that was being carried out.

1.2 Experiment 1 - Task design

In the first experiment (Figure 2), participants were required to encode and maintain a set of features from an array of compound stimuli. Each compound stimulus was composed of a pseudo-randomly assigned Arabic digit, spatial position and abstract fractal. Each trial began with a pre-encoding cue directing participants to focus the features from one of the three stimulus domains (Numbers, Position or Object). Then, three, five or seven compound stimuli were presented within a 5-by-5 grid. After 10 seconds of encoding, all compound stimuli were removed and the participants were required to maintain the cued domain features (e.g. number, positions or objects). Following the delay, the previous compound stimuli were presented again with one replaced digit, spatial position and fractal. Only a single domain feature was replaced in any one of the compound stimuli. Participants were then required to select the compound stimulus that contained the new feature from the cued domain. The trial terminated earlier if the participants responded within the allotted 10-seconds. Another trial began after an additional 10-second post-response interval.

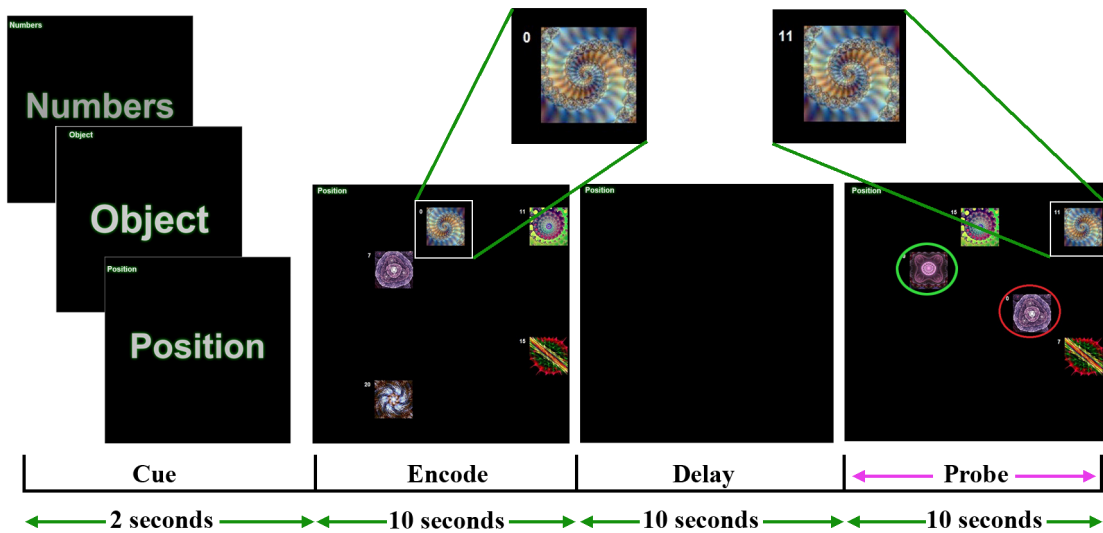


Figure 2: Task design of experiment 1. In this example, participants were required to remember the spatial position of the compound stimuli. As such, when presented with the probe array after the delay period, they were required to select the stimulus that was in a different position compared to the encoded array. Here the correct answer was the object circled in red. However, if participants were required to remember the fractal features of the compound stimuli, they would select the green circled object because it was not present in the encoding array. Similarly, if participants were required to remember the number features, they would choose a different compound stimulus with a new number that was not present in encoding array. On each trial, one Arabic number, spatial position, and fractal differed between the encoding and probe arrays of different compound stimuli.

1.3 Experiment 2 - Task design

The second experiment (Figure 3) was similar to the first in design; however, participants were required on some trials to manipulate information in mind as opposed to simply maintain. Each trial began with a pre-encoding cue directing participants to focus on a specific stimulus feature (Numbers or Position; N.B. – Fractal shapes were not used in this task). Subsequently, either three or six Arabic digits were pseudo-randomly presented on a 5-by-5 spatial grid. A second post-encoding cue was then presented to inform participants to either maintain or manipulate the encoded information. If the maintain cue was presented, participants simply needed to remember the Arabic digits or spatial positions in order to find the new cued stimulus feature during their respective trials. In contrast to the previous experiment, if the manipulate cue was presented, participants needed to add three to every encoded digit during number trials or rotate the entire spatial grid by 90-degree clockwise during position trials. The transformed stimulus set was then presented after a delay with an altered Arabic digit and spatial position. Participants were required to select the non-matching feature based on the stimulus domain and manipulation that was cued throughout the trial. The trial terminated earlier if the participants responded within the allotted 10-seconds. Another trial began after an additional 10-second post-response interval.

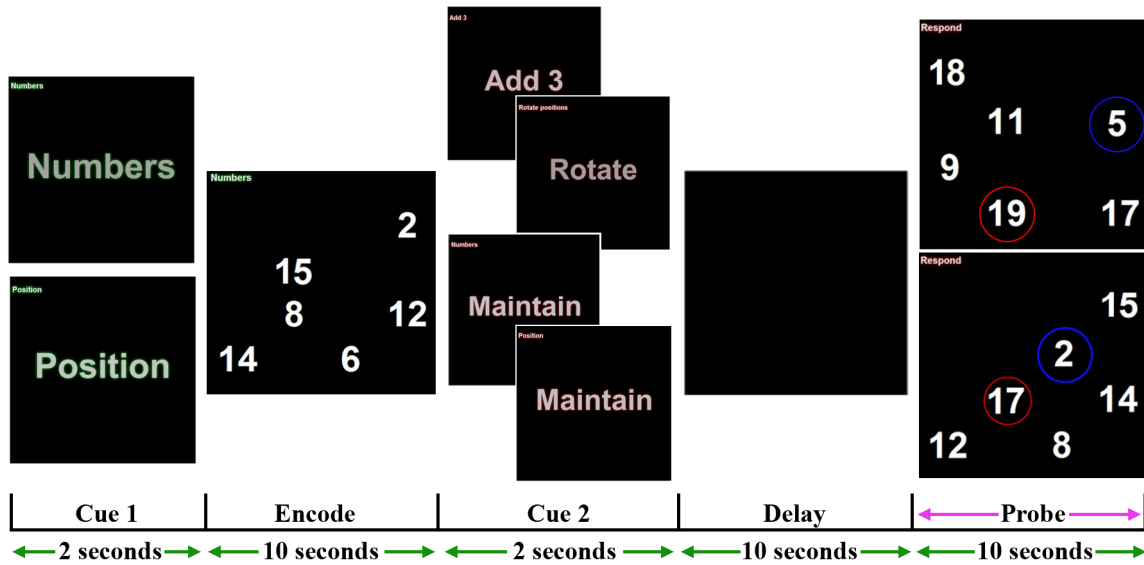


Figure 3: Task design of experiment 2. In this example, participants were cued to focus on the identity of the Arabic numbers whilst ignoring spatial positions. After encoding, participants were required to maintain (lower images) or manipulate (upper images) information. If required to maintain, they had to remember the numbers or spatial positions during their respective trials and then select the new digit (red) or position (blue) after the delay. In contrast, if participants had to manipulate, they were then required to add three to every encoded digit during number trials or rotate the entire spatial grid by 90-degrees clockwise during position trials. After the delay, the transformed stimulus set was presented again with an altered digit (blue) and position (red). Participants were allocated 10 seconds to select the non-matching feature based on the two cues presented throughout the trial.

1.4 Participants

In the first experiment, nineteen right-handed volunteers between the ages of 20 to 40 with corrected to normal vision and no history of neurological or psychiatric illnesses participated in the fMRI study. All participants consented to experimental procedures and underwent a short training session to ensure that they understood and were capable of performing the task. The training session consisted of one block of the task (approximately 15-20 minutes) undertaken on a laptop outside of the MRI scanner. In the second experiment, sixteen right-handed participants were recruited and trained using the same criteria.

1.5 Data acquisition

In both experiments, data were collected in three blocks of scanning acquisition. In the first experiment, each block contained 18 trials, two each from nine possible combinations of stimulus domains (Number, Position and Shape) and WM loads (3, 5 and 7). In the second experiment, each block contained 16 trials, two each from eight possible combinations of cognitive processes (Maintenance and Manipulation), stimulus domains (Number and Position) and WM load (3 and 6).

MRI scanning was conducted at the Robarts Research Institute at Western University in Canada using a 3-Tesla Siemens Trim Trio scanner. Thirty-two 3-mm slices (0.75 mm inter-slice gap and interleaved slice order) were acquired using a repetition time (TR) of 2 seconds and in-plane resolution of 3×3 mm. Approximately 300-400 T_2^* -weighted echo-planar images depicting blood oxygen level-dependent (BOLD) contrasts were acquired from each participant depending on their reaction times. The first ten images were discarded to avoid T_1 equilibrium effects. Using a mirror mounted to the head-coil, stimuli presented on a back-projection screen were visible from the bore of the MRI scanner. Responses were taken with a custom MRI-compatible trackball mouse. Both WM paradigms were programmed using Adobe Flash Builder 4.5 and embedded in a scanner interface programmed in Visual Basic 6.

Brain images were pre-processed and analysed using the Statistical Parametric Mapping 5 software package (SPM5, Wellcome Department of Cognitive Neurology). The images were reoriented to correct for participant motion, spatially normalised to the standard Montreal Neurological Institute template, smoothed with an 8-mm full-width at half-maximum Gaussian kernel and high-pass filtered (cut-off period 180 s).

1.6 Independent Components Analysis

A spatial group ICA was conducted on the pre-processed functional data from all participants using the Group ICA of fMRI toolbox for MATLAB (GIFT – MIND Research Network, Albuquerque, United States). Prior to the use of ICA, data were pre-processed by removing mean-per-time points using GIFT. In order to identify the functional networks within MD regions that were consistently recruited across participants, 10-mm radius ROIs based on peak coordinates for the bilateral IFS (-41; 23; 29 and -41; 23; 29), AIFO (-35; 18; 2 and 35; 18; 2), IPS (-37; -56; 41 and 37; -56; 41) and ACC/SMA (0, 31, 24) were combined and the ICA was undertaken within that mask. The information maximization (Infomax) algorithm was then used to extract group spatial components. In order to ensure the reliability of the spatial decomposition, the ICA was repeated 100 times with random initial weights using the GIFT ICASSO tool. Group component time-courses were then back-reconstructed using the GIFT GICA3 method. Here, the ICA was set to extract two components as prior research (Hampshire *et al.*, 2012) indicated that MD regions house a dorsal (IFS-IPC) and ventral (AIFO-ACC) sub-networks. Peak coordinates from the extracted mean components were then used to generate ROIs using the MarsBar toolbox (<http://marsbar.sourceforge.net>), which averages data across all voxels within a given region.

1.7 Fixed and Random Effects Analyses

Both fixed- and random-effects analyses were completed using SPM5. Separate fixed-effects analyses were carried out on the individual participant data and analysed using general linear modelling. In the first experiment, 45 regressors were generated using trial events that were specific for the stimulus domain (Numbers, Position, and Shapes), load (3, 5, and 7) and stage (Cue, Encode, Delay, Response, and Rest). In the second experiment, 40 regressors were generated using trial events that were specific for stimulus domain (Numbers and Position), load (3 and 6), cognitive process (Maintenance and Manipulation) and stage (Cue, Encode, Delay, Response and Rest). Six movement regressors and a resting baseline constant were also added into the model of both experiments.

All regressors were created by convolving the onsets and durations of each event using a canonical hemodynamic response thus ensuring that beta-values represented an estimate of the neural response per unit time. Beta-weighted images from different stimulus domains, WM loads and/or cognitive processes were examined at the group level using random-effects analyses in order to show brain regions that were differentially activated when different trial types were contrasted. T-tests were then used to compare the mean voxels for a specific stimulus domain, load and/or cognitive process for the ROIs generated by the ICA.

1.8 Experiment 1: Behavioural Results

All 19 participants completed three blocks of 18 trials. The effects of stimulus domain (Numbers, Position or Objects) and load (3, 5 or 7) on reaction times (RT) (Figure 4a) were examined using a 3×3 repeated-measures analysis of variance (ANOVA). The findings revealed a significant interaction between domain and load ($F_{4, 72} = 2.651, p < 0.05$) as seen in the line graph of figure 4a. Noticeably, the interaction is mostly driven by a greater effect of load on number and object trials than position.

Using a similar 3×3 repeated measures ANOVA, the effects of stimulus domain and load on the total number of correctly solved problems were also examined (Figure 4b). There was only a significant main effect of load ($F_{1,338, 24,083} = 11.850; p < 0.01$) such that significant decreases in accuracy were present when contrasting medium- ($p < 0.05$) and low-load trials ($p < 0.001$) to high-load trials. No significant main effects of stimulus domain ($p > 0.08$) or interacting effects ($p > 0.1$) of load and stimulus domain were present.

In order to examine the domain-specific brain activations without the effects of general difficulty, accuracy-matched trials (Number-5, Position-7 and Object-3) were selected for neuroimaging contrasts.

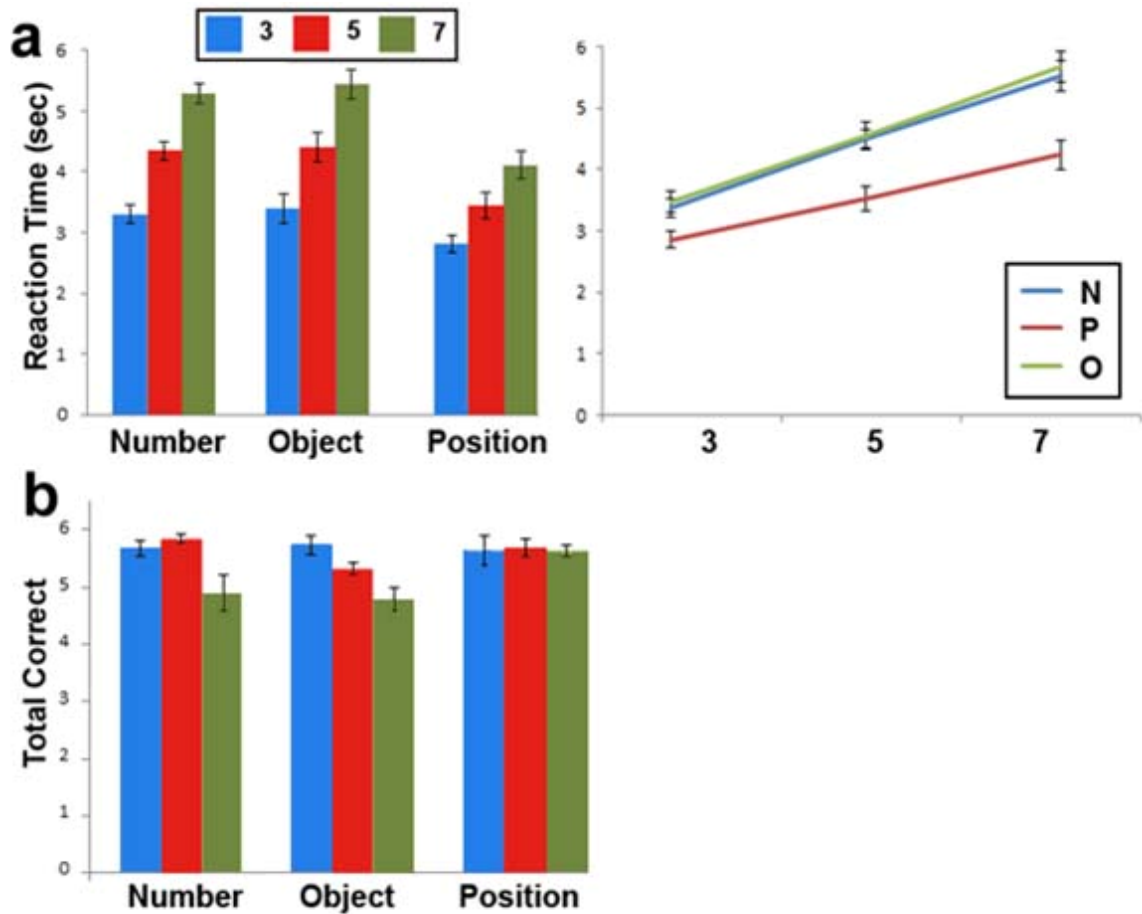


Figure 4: Behavioural results from experiment 1. (a) Mean RT with the standard error of the mean. There was a significant interaction between domain and load as seen on the left image. Load has a greater effect on RT for object and number trials than the position trials. (b) Mean number of correct responses (out of a total of 6). There was a significant main effect of load such that increasing load significantly decreased the number of correctly solved problems. ($*p < 0.05$, $**p < 0.01$, $***p < 0.001$) Error bars represent standard error of the mean.

1.9 Experiment 1: Neuroimaging Results

A two-component ICA of MD regions was used in this experiment because our previous factor analysis study (Hampshire *et al.*, 2012) showed that only two statistically significant components accounted for ~90% of the variance. As predicted, the results generated two networks (Figure 5) that were highly similar to the previous results. Peak coordinates were recorded for these networks and they were used to generate ROIs. Specifically, a ventral component encompassed bilateral AI/FO (-34; 18; 2 and 35; 19; 3) and bilateral ACC/SMA (-5; 23; 34 and 6; 23; 36) whilst a dorsal component covered bilateral IPS (-35; -59; 41 and 35; -58; 40) and right IFS (45; 14; 32). In order to explore the functional contributions of these two networks, the data were examined using two separate 3 x 3 full factorial designs for encoding and delay in SPM5. Factors included stimulus domain (Number, Position and Objects) and load (3, 5 or 7 items).

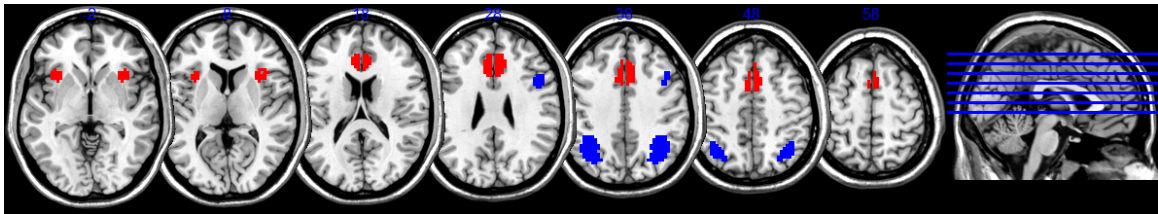


Figure 5: Extracted ICA components from experiment 1. The ventral network (red) recruited the bilateral AI/FO and SMA/ACC whilst the dorsal network (blue) recruited the right IFS and bilateral IPS.

1.10 Experiment 1: ROI results

During the encoding period, strong activation was present for all levels of load and stimulus domain within both networks. There was a significant main effect of load on the BOLD signals within both ventral ($F = 5.61, p < 0.01$) and dorsal ($F = 5.76, p < 0.01$) networks (Figure 6a). Pairwise comparisons revealed that increased BOLD signals were observed during high-load trials within both ventral (low versus high load $t = 2.74, p < 0.01$; medium versus high load $t = 3.28, p < 0.01$) and dorsal networks (low versus high load $t = 3.30, p < 0.01$; medium versus high load $t = 2.84, p < 0.01$). In addition, there was a significant main effect of stimulus domain on the BOLD signals within the ventral network ($F = 10.72, p < 0.001$). Pairwise comparisons revealed that increased BOLD signals were observed during object trials in contrast to number ($t = 3.12, p < 0.01$) and position ($t = 4.54, p < 0.001$) trials (Figure 6b). No significant main effect of domain was observed in the dorsal network ($p > 0.95$). Furthermore, no significant interacting effects of domain and load were present in either ventral ($p > 0.09$) or dorsal networks ($p > 0.39$).

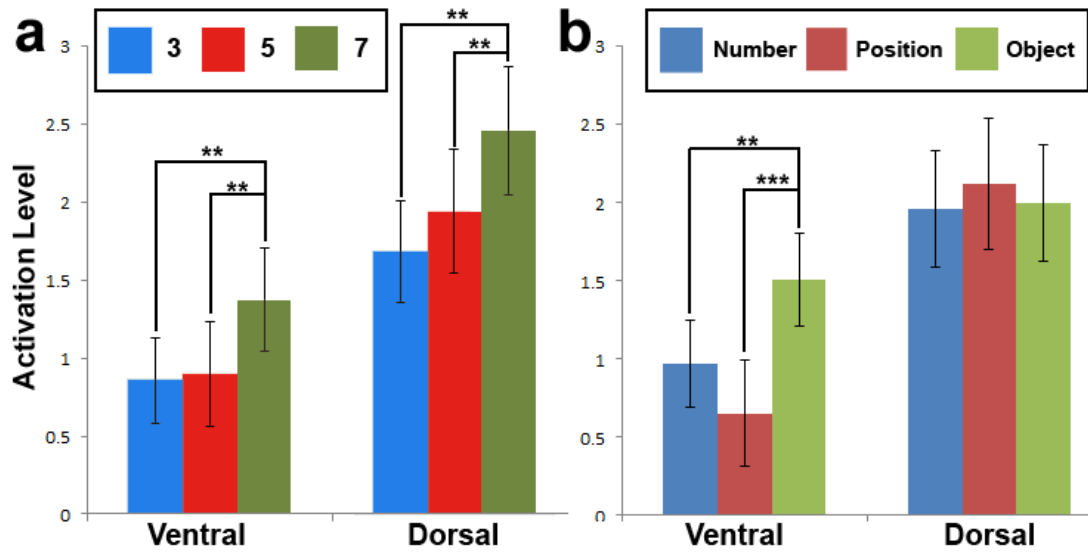


Figure 6: ROI analyses during encoding period of experiment 1. (a) Beta-weights for each level of load. Significant increased BOLD signal was observed during high-load (7-items) trials within both ventral and dorsal networks. (b) Beta-weights for each level of domain. Despite significant activation across all levels of domain for both networks, only increased BOLD signals were observed during object trials within the ventral network. (** $p < 0.01$, *** $p < 0.001$) The error bars represent standard error of the mean.

During the delay period, robust activation was evident within both networks for all levels of load (Figure 7a) and stimulus domains (Figure 7b). No significant main effects of load were present in the ventral ($p > 0.83$) and dorsal ($p > 0.69$) networks. There was a significant main effect of domain on the BOLD signals within the ventral network ($F = 6.57, p < 0.01$). Specifically, increased BOLD signals were observed when contrasting object trials against number ($t = 3.48, p < 0.001$) and position trials ($t = 2.78, p < 0.01$). No significant main effect of domain ($p > 0.07$) was observed in the dorsal network. Furthermore, no significant interacting effects of load and domain were present in the ventral ($p > 0.98$) and dorsal networks ($p > 0.88$).

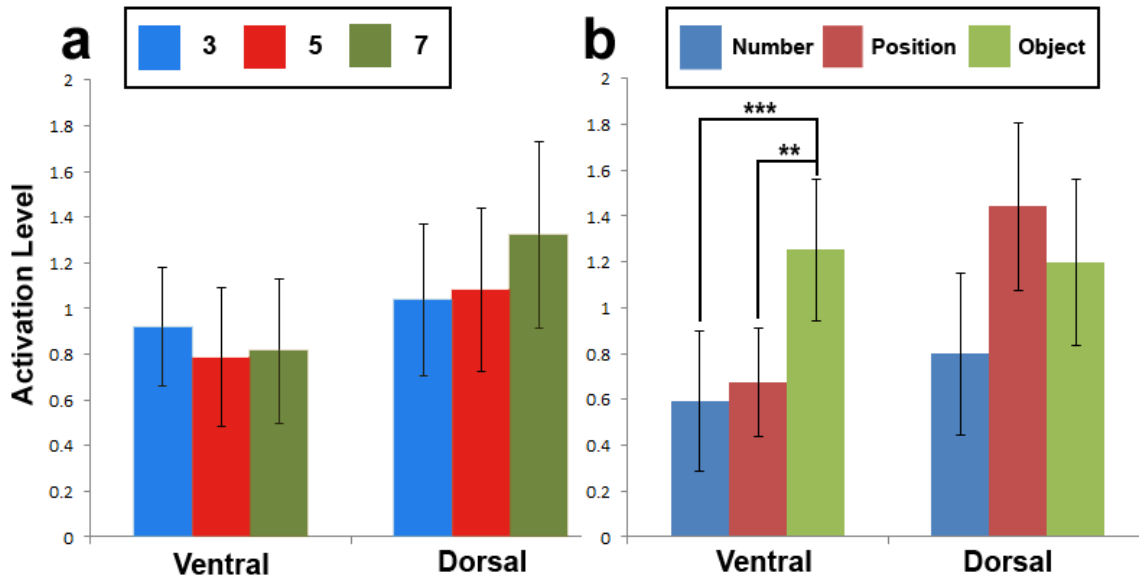


Figure 7: ROI analyses during the delay period of experiment 1. (a) Beta-weights for each level of load. Significant activations were evident for all levels of load with no significant differences across levels. (b) Beta-weights for each level of domain. Increased activation was evident within the ventral network during object vs. number and position trials (* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$). Error bars represent standard error of the mean.

To test whether or not the significant increased BOLD signals within the ventral network during object trials were due to general difficulty rather than domain specific activation, accuracy-matched activations were contrasted. A correlation coefficient matrix (Table 1) was conducted on the number of correct responses for each trial condition of every subject. The trial conditions that had the highest correlation coefficients were used in the subsequent accuracy-matched ROI analyses. In particular, BOLD signals from medium-load position (P5) and medium-load number trials (N5) were contrasted against the BOLD signals from low-load object trials (O3) (Figure 8).

During encoding, significant increased BOLD signals were present when contrasting object against number trials ($t = 2.838$, $p < 0.05$) and position trials ($t = 2.643$, $p < 0.05$). During the delay, significant increased BOLD signals were observed when contrasting object against number ($t = 3.146$, $p < 0.01$) but not position trials ($t = 1.942$, $p = 0.068$). Thus, it appears that the ventral network is sensitive to non-verbal and non-spatial object stimuli. However, given that the ventral network was also activated during position and number trials, this difference is statistical as opposed to absolute.

Table 1: Correlation Matrix of Accuracy Results. The listed values are the correlation coefficients when comparing the number of correct responses for specific trial conditions. The highest correlation coefficients (in green) were subsequently used for the accuracy-matched ROI analyses.

	O3	O5	O7
N3	0.09	-0.01	0.13
N5	0.40	0.33	0.16
N7	0.22	-0.15	-0.11
P3	0.24	0.13	0.11
P5	0.36	0.05	0.18
P7	0.03	-0.26	-0.22

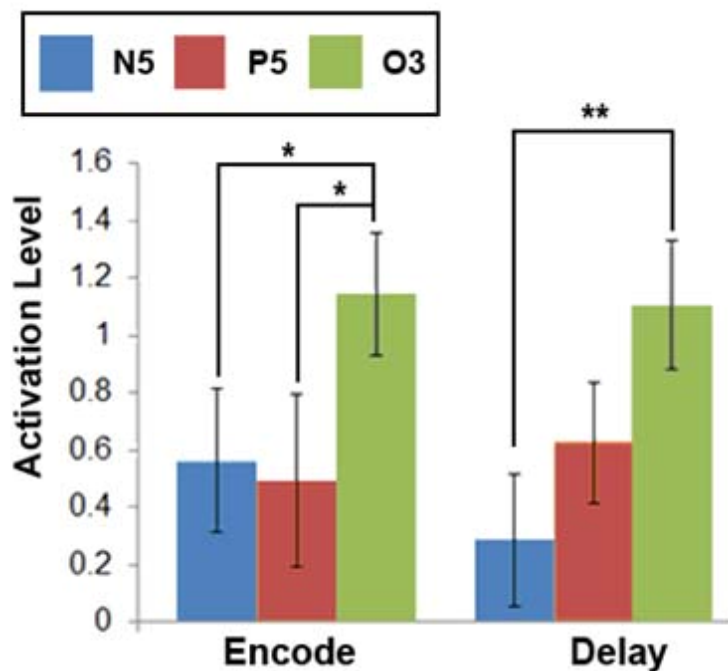


Figure 8: Accuracy-matched contrasts within the ventral network. The figure illustrates the beta-weights for low load (3-items) objects, medium load (5-items) positions and medium-load (5-items) numbers during the encoding and delay periods within the ventral network. There is greater activation for object trials relative to number and position trials during encoding and delay within the ventral network even when controlling for general difficulty. Error bars represent standard error of the mean.

1.11 Experiment 1: Whole brain analyses

Voxel-wise whole brain analyses were used to identify the brain regions that were specific to certain stimulus domains and load. Contrast maps comparing each of the experimental conditions to baseline were generated for individual participants and entered into group-level random-effects analyses. Data from the encoding and delay periods were analysed using a 3x3 factorial design with load and stimulus domain as factors. A subsequent conjunction analysis of object against number contrast and object against position contrast was conducted to find overlapping object-specific regions. Similar conjunction analyses were also used to find position and number-specific brain areas.

Examination of the domain-specific results during the encoding stage (threshold corrected using false discovery rate, FDR, of $p < 0.05$) showed that posterior and anterior areas were sensitive for spatial and non-spatial processing, respectively (Figure 9 – upper image). In addition, left-hemispheric regions were sensitive for number trials. Likewise, analyses that examined the main effects of domain during the delay period (threshold corrected using FDR of $p < 0.05$) also revealed similar dorsal and ventral areas sensitive for spatial and non-spatial processing. However, number-specific activations were not present at the corrected threshold during maintenance (Figure 9 – lower image). Baseline activation of trials separated by domain during the encoding (Figure 10) and delay periods (Figure 11) indicates that the frontoparietal network is strongly active regardless of stimulus domains.

Examinations of load effects during the encoding stage (threshold corrected using FDR of $p < 0.05$) showed that when contrasting high- against low-load trials, primary visual and DLPFC areas are recruited (Figure 12, **Error! Reference source not found.**Table 2) in line with previous research (D'Esposito *et al.*, 2000). Interestingly, contrasts comparing high- against low-load trials during the delay stage showed no significant differences.

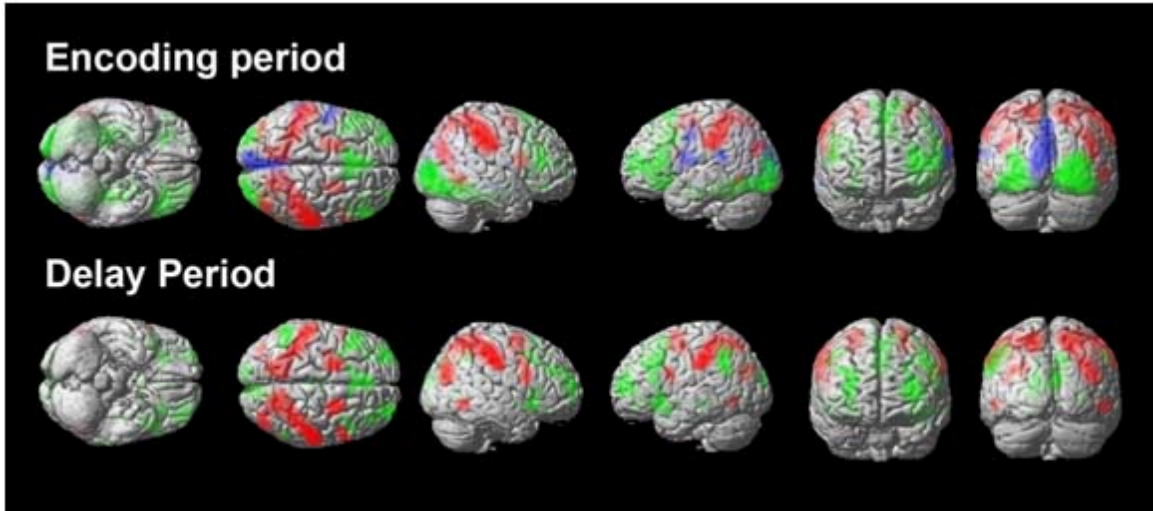


Figure 9: Whole-brain analyses of stimulus-specific activations. The figure depicts whole-brain maps from group-level analyses with FDR correction at $p < 0.05$. Conjunction analyses of activations during object trials against number and object trials against position are shown in green. Similar conjunction analyses were applied to position (red) and number trials (blue).

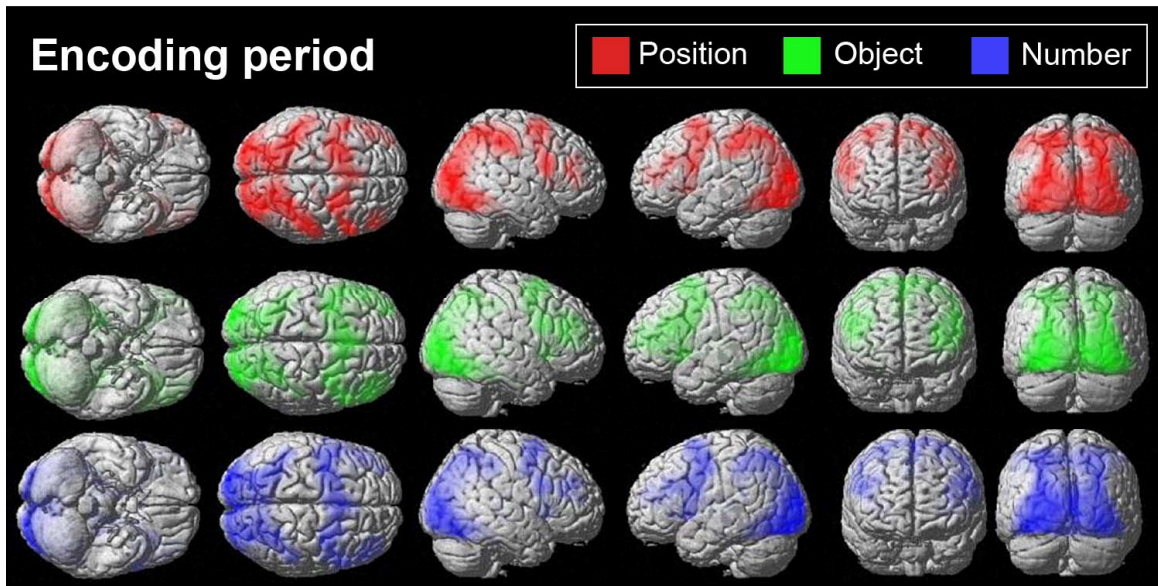


Figure 10: Baseline activation during the encoding period of trials separated by domain. The figure depicts whole-brain maps from group-level analyses with FDR correction at $p < 0.05$.

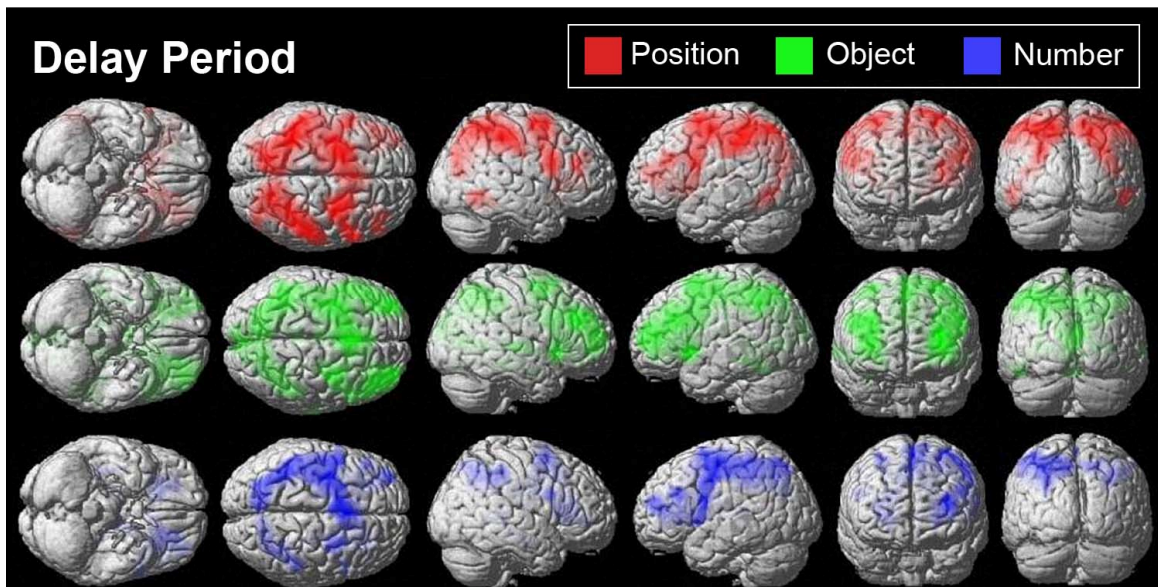


Figure 11: Baseline activation during the delay period of trials separated by domain. The figure depicts whole-brain maps from group-level analyses with FDR correction at $p < 0.05$.

Table 2: Peak activation coordinates from whole brain analysis of experiment 1.

Trial Type	x	y	z	t	Region	BA
Verbal > Object	-12	-87	3	9.95	L Calcarine	17
Verbal > Position	-3	-84	15	8.94	L Calcarine	18
Encoding Period	-9	-57	0	8.00	L Lingual	18
	-51	-6	42	7.42	L Post central	6
	-63	3	21	6.54	L Post central	43
	-57	-42	18	5.66	L Superior Temporal	42
	-21	-27	-3	4.49	L Hippocampus	-----
Position > Object	63	-24	42	10.7	R. Supramarginal	1
Position > Verbal	-60	-27	39	10.3	L. Supramarginal	2
Encoding Period	-15	-63	60	7.73	L Precuneus	7
	-24	-9	54	7.67	L superior frontal	6
	24	-6	57	7.06	R superior frontal	6
	51	6	18	6.98	R Rolandic Operculum	6
	-39	-81	30	6.03	L Mid Occipital	19
Object > Position	-57	-54	39	4.83	L. Inferior Parietal	40
Object > Verbal	-33	60	15	4.55	L. Mid Frontal	10
Encoding Period	-3	30	39	4.16	L. Medial Superior Frontal	32
	-12	-96	21	3.50	L. Superior Occipital	18
	24	30	-15	3.96	R. Inf. Frontal. Orb	11
	36	24	9	3.89	R. Inf. Frontal Tri.	48
	30	60	18	3.67	R. Superior Frontal	10
Load effects (High > Low)	9	-90	6	16.73	R. Calcarine	17
Encoding Period	-27	-3	51	7.17	L. Mid Frontal	6
	27	0	48	6.62	L. Mid Frontal	6
	-45	3	30	6.48	L. Precentral	44
	45	6	27	5.12	R. Precentral	44
	33	21	9	4.52	R. Insula	48
Position > Object	42	-36	45	7.67	R. Supramarginal	2
Position > Verbal	-18	-63	57	7.48	L Superior Parietal	7
Delay Period	-21	-3	60	6.94	L Superior Frontal	6
	51	6	39	5.53	R. Precentral	6
	-54	6	24	5.24	L. Precentral	6
	54	-60	-6	5.23	R. Inferior Temporal	37
	-24	-72	30	4.56	L. Mid Occipital	19
Object > Position	-6	-15	27	5.05	-----	----
Object > Verbal	30	60	21	4.67	R. Mid Frontal	----
Delay Period	-33	57	18	4.46	L. Superior Medial Frontal	46
	-45	15	-9	3.69	Left Insula	----
	30	-30	-6	3.61	R. Hippocampus	20

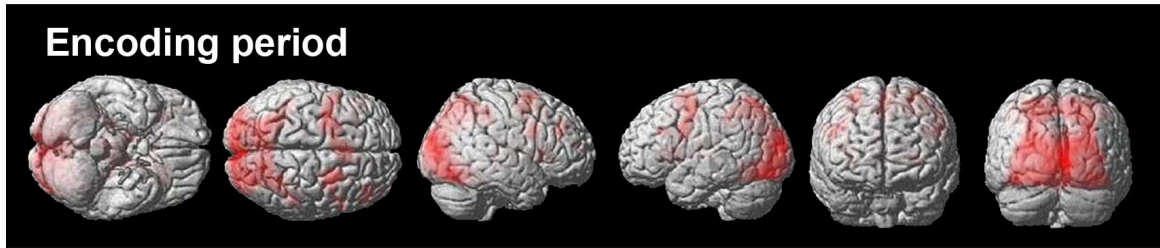


Figure 12: Whole-brain analysis of load-specific activations during encoding. This figure depicts whole-brain maps from group analyses with FDR correction at $p < 0.05$.

1.12 Experiment 2: Behavioural Results

All 16 participants completed three blocks of 16 trials. The effects of cognitive process (maintenance or manipulation), stimulus domain (Number or Position) and load (three or six) on RT (

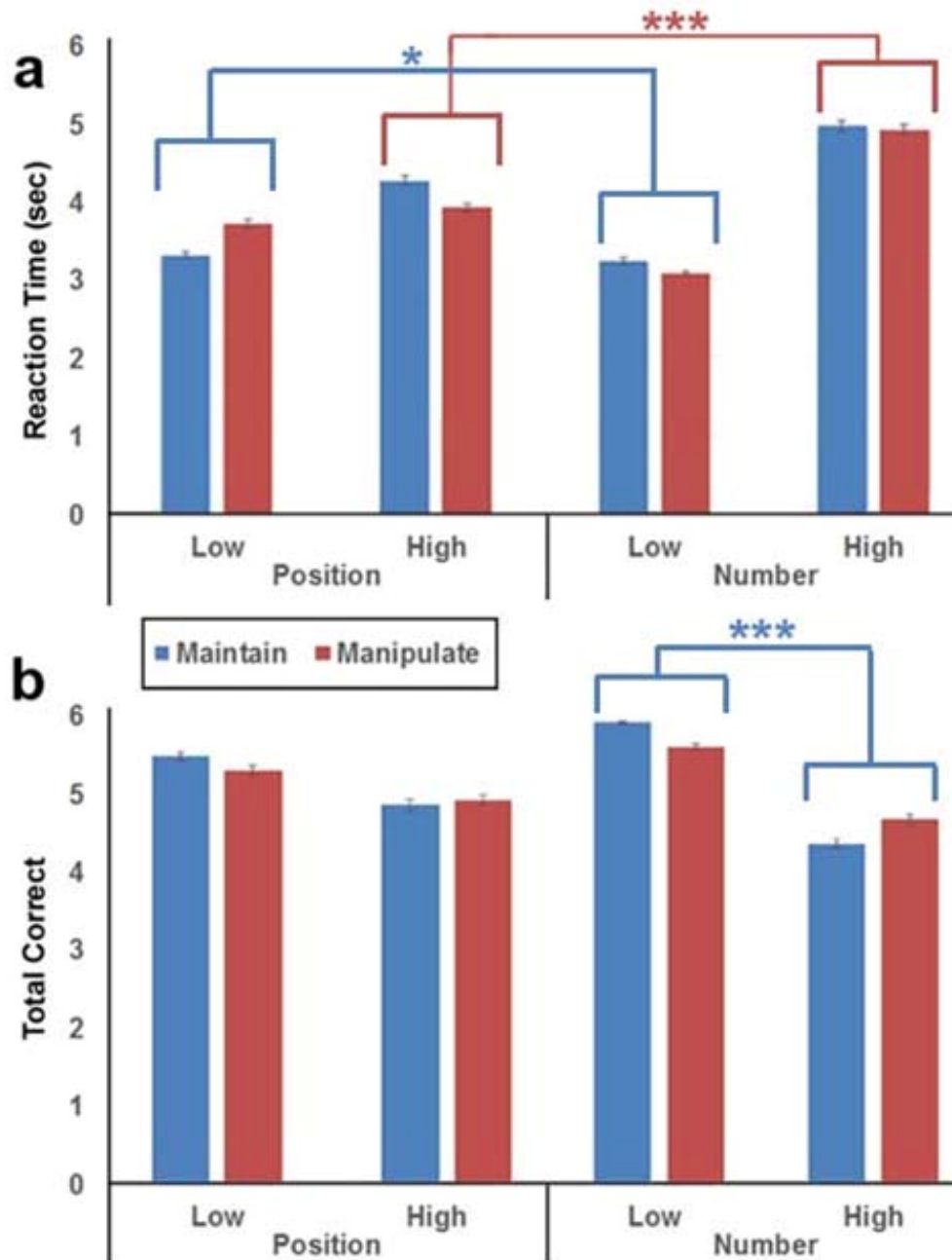


Figure 13a) were examined using a $2 \times 2 \times 2$ repeated-measures ANOVA. Results revealed a significant interaction between stimulus domain and load ($F_{1,15} = 26.1$;

$p < 0.001$). Further pairwise comparisons revealed that at low loads, RTs of number trials are significantly shorter than RTs of position trials ($p < 0.05$). However, at high-load, RTs of number trials are significantly longer than RTs of position trials ($p < 0.001$). No significant main ($p > 0.7$) effect of RT by the type of cognitive processes was observed. Furthermore, no interacting effects of RT by the cognitive process type and load ($p > 0.2$), cognitive process type and domain ($p > 0.4$) or three-way interactions were present ($p > 0.08$).

Using a similar repeated measures ANOVA, the effects of all three factors on the total number of correctly solved problems (

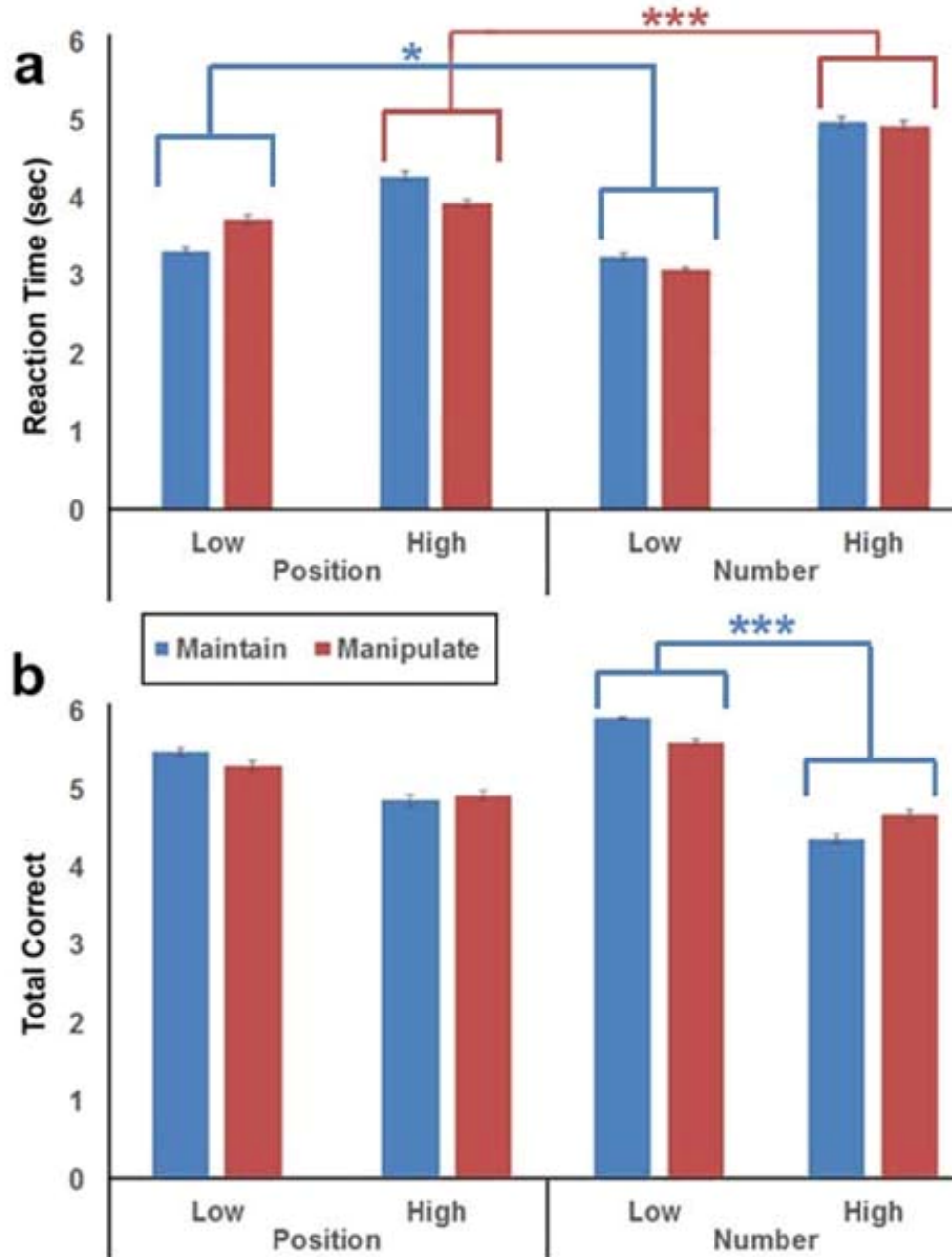


Figure 13b) were also examined. There was a significant interaction between stimulus domain and load ($F_{1,15} = 6.429, p < 0.05$) such that the accuracy of number trials was significantly lower during high rather than low-load trials ($p < 0.001$). In contrast, accuracy of position trials showed no significant differences between different loads ($p > 0.07$). Surprisingly, no significant main effect of cognitive process type was observed (p

> 0.8). In addition, no interacting effects of accuracy by cognitive process type and load ($p > 0.069$), cognitive process type and domain ($p > 0.8$) or three-way interactions were present ($p > 0.4$).

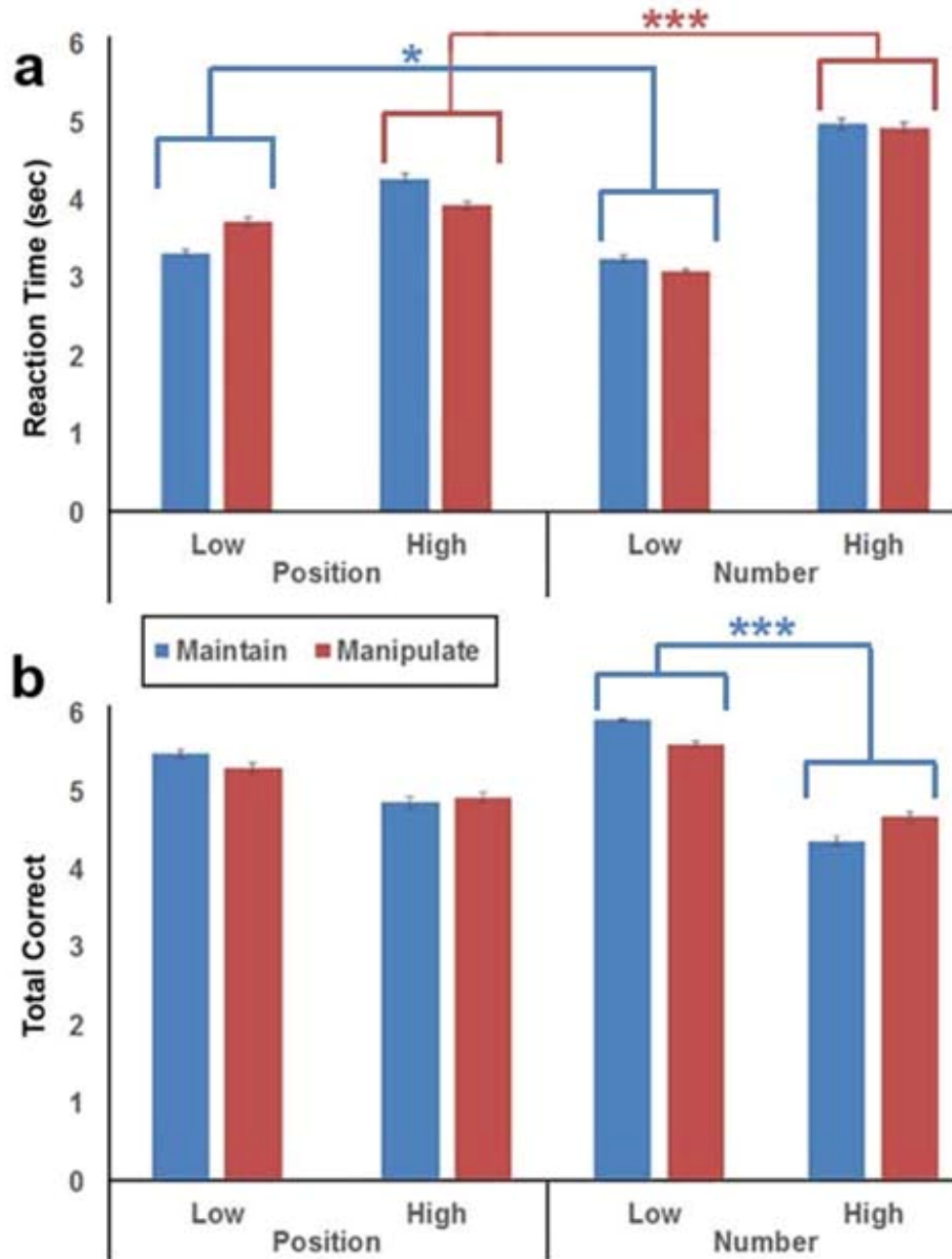


Figure 13: Behavioural results from experiment 2. (a) Mean RTs with the standard error of the mean. There was a significant interaction between stimulus domain and load. There were no significant main or interacting effects by the cognitive process type. (b) Mean number of trials correct (out of a total of 6) with the standard error of the mean. There was a significant interaction between stimulus domain and load such that accuracy significantly decreased during number trials at higher loads. (* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$) Error bars represent standard error of the mean.

1.13 Experiment 2: Neuroimaging Results

As in the previous experiment, two MD sub-networks were extracted when applying a two-component ICA with a mask of MD regions (Figure 14). These networks were similar to the reasoning and short-term memory networks documented in previous publication (Hampshire *et al.*, 2012). Using these two component maps, significant peak coordinates were recorded and used for ROI analyses. In detail, component one consisted of bilateral IPS (-35; -58; 40 and 35; -58; 40), right IFS (44; 16; 33) and dorsal areas of the ACC/SMA (5; 9; 49 and -4; 8; 49) whilst component two consisted of bilateral AI/FO (-34; 18; 3 and 35; 19; 4) and bilateral ACC/SMA (-5; 23; 35 and 6; 23; 37). In order to explore the functional contributions of these two networks, data were examined using two 2 x 2 x 2 full factorial designs for encoding and delay periods in SPM5. Stimulus domain (Number or Position), WM load (3 or 6 items) and cognitive process type (Maintenance or Manipulation) were included as factors.

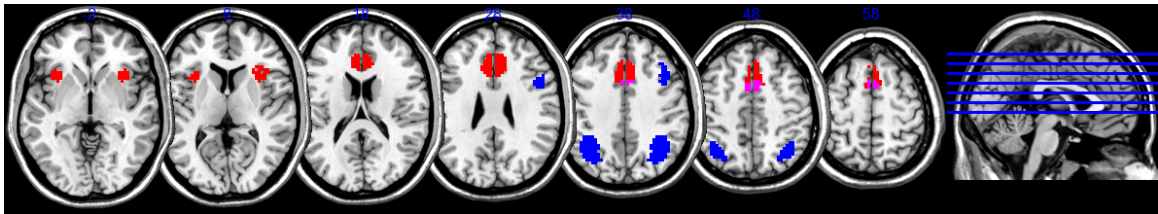


Figure 14: Extracted ICA components from experiment 2. The ventral network (red) recruited bilateral AI/FO and SMA/ACC whilst the dorsal network (blue) recruited the right IFS, bilateral IPS and dorsal SMA/ACC.

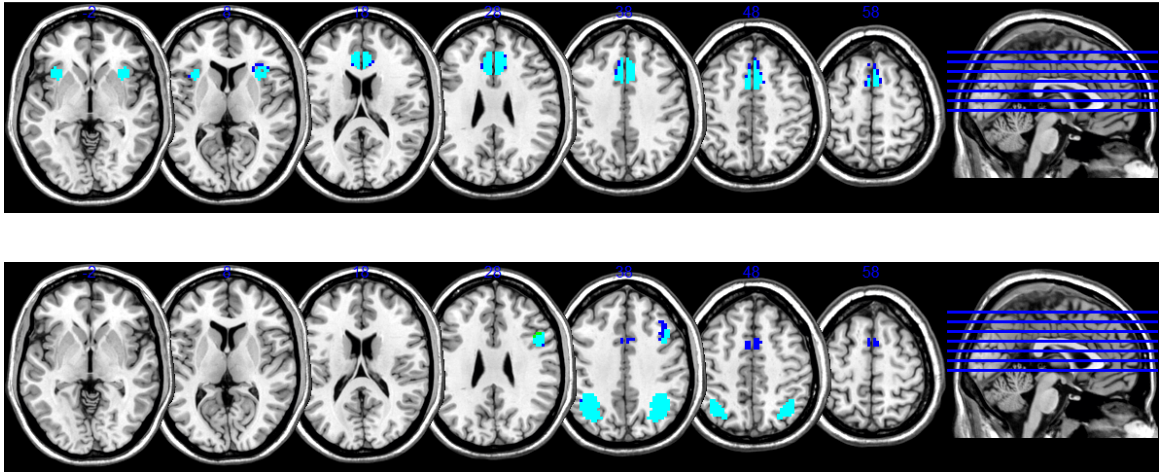


Figure 15: Overlapped components from both experiments. This figure depicts the extracted ventral (Bottom) and dorsal (Top) components from experiment 1 (green), experiment 2 (blue) or overlapped (cyan).

1.14 Experiment 2: ROI results

During the encoding period, there was robust activation in the ventral (Figure 16a) and dorsal networks (Figure 16b). Specifically, there were significant main effects of load in the ventral ($F = 5.93$; $p < 0.05$) and dorsal networks ($F = 14.05$; $p < 0.001$). Increased BOLD signals were observed during high load trials for both ventral ($t = 2.43$; $p < 0.05$) and dorsal networks ($t = 3.75$; $p < 0.001$). This is in line with our previous experiment, which showed increased BOLD signals in the ventral and dorsal networks during high-load trials. Despite strong activation, no additional main effects of stimulus domain were present in both ventral ($p > 0.38$) and dorsal networks ($p > 0.35$). Furthermore, no interacting effect of the BOLD signal by stimulus domain and load was present in either ventral ($p > 0.75$) or dorsal networks ($p > 0.17$).

Given that participants did not know whether to manipulate or maintain information during the encoding stage, we anticipated that there would be no effect of cognitive process types. As expected, no main effect of the BOLD signal was observed in either the ventral ($p > 0.21$) or dorsal ($p > 0.18$) networks. Furthermore, no interactions between the domain and cognitive process type ($p_{ventral} > 0.13$; $p_{dorsal} > 0.10$), nor load and cognitive process type ($p_{ventral} > 0.19$; $p_{dorsal} > 0.08$) were observed. There were also no significant three way interaction for either ventral ($p > 0.29$) or dorsal networks ($p > 0.78$).

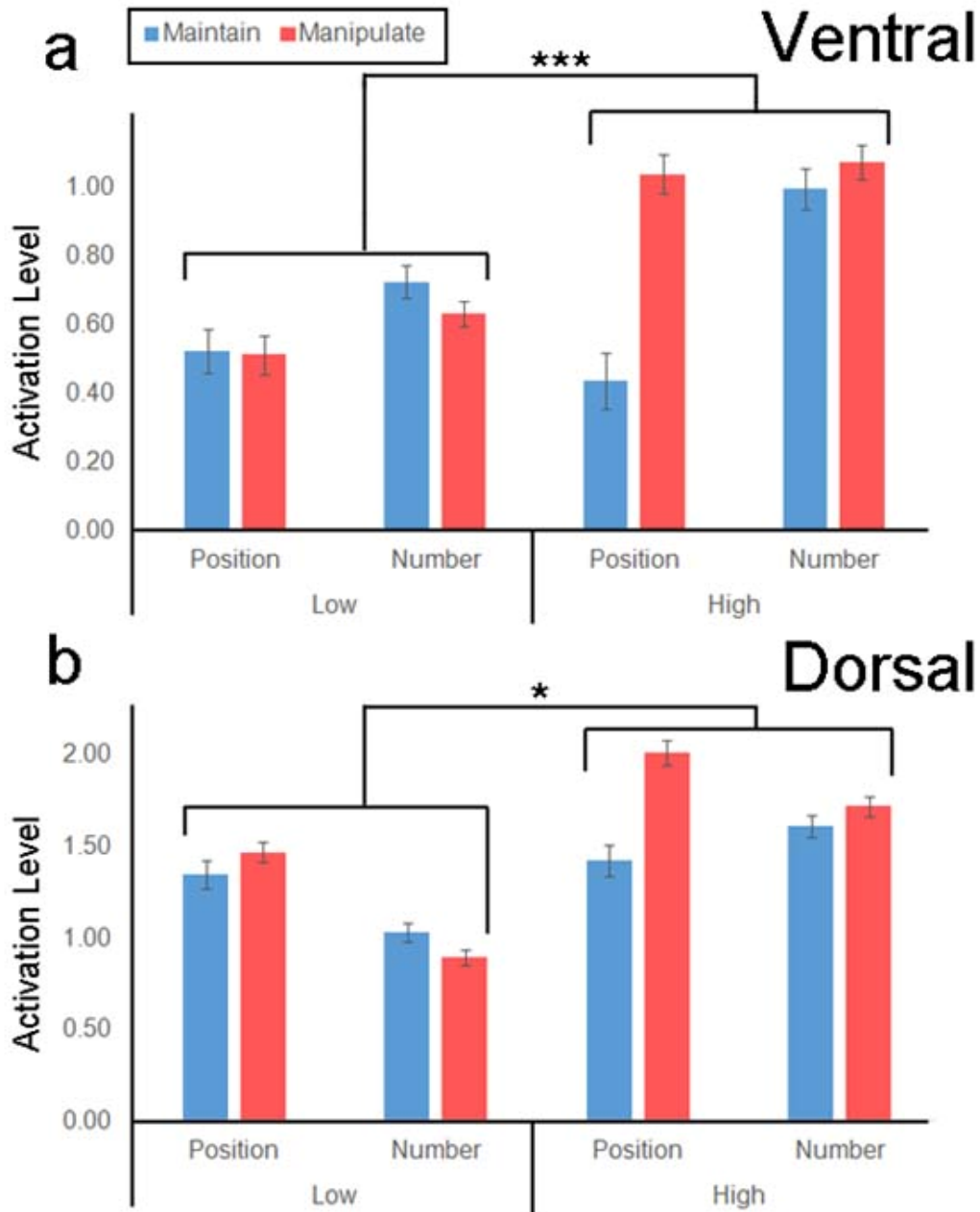


Figure 16: ROI analyses during the encoding period of experiment 2. (a) Beta-weights for ventral network. (b) Beta-weights for dorsal network. For both ventral and dorsal networks, there was significantly increased BOLD signal as load increased. No other significant main or interacting effects of domain or type of cognitive function were present. (* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$) Error bars represent standard error of the mean.

During the delay, there was significant activation for all levels of load, stimulus domain and cognitive process types within the ventral and dorsal networks. Within the ventral network (Figure 17a), there was a significant interaction of load and stimulus domain ($F = 10.19, p < 0.01$). Pairwise comparisons revealed that there was a significant effect of load for number but not position trials such that increased BOLD activity was observed during high-load number trials ($t = 3.49, p < 0.001$). No main effect of cognitive process types was present in the ventral network. Furthermore, no interacting effects between the load and cognitive process type ($p > 0.20$), stimulus domain and cognitive process type ($p > 0.80$) were evident. The three-way interaction was also not present ($p > 0.87$).

More importantly, within the dorsal network (Figure 17b), there was a significant interaction effect of load during manipulation trials but not maintenance ($F = 7.01, p < 0.05$). Increased activation was observed during high-load manipulation trials ($t = 2.46, p < 0.001$). In addition, there was a significant main effect of domain present in the dorsal network ($F = 6.78; p < 0.05$) such that increased BOLD signals were present during position trials ($t = 2.60; p < 0.01$). However, no interaction between domain and cognitive process type ($p > 0.22$) was present. The three-way interaction was also not present ($p > 0.74$).

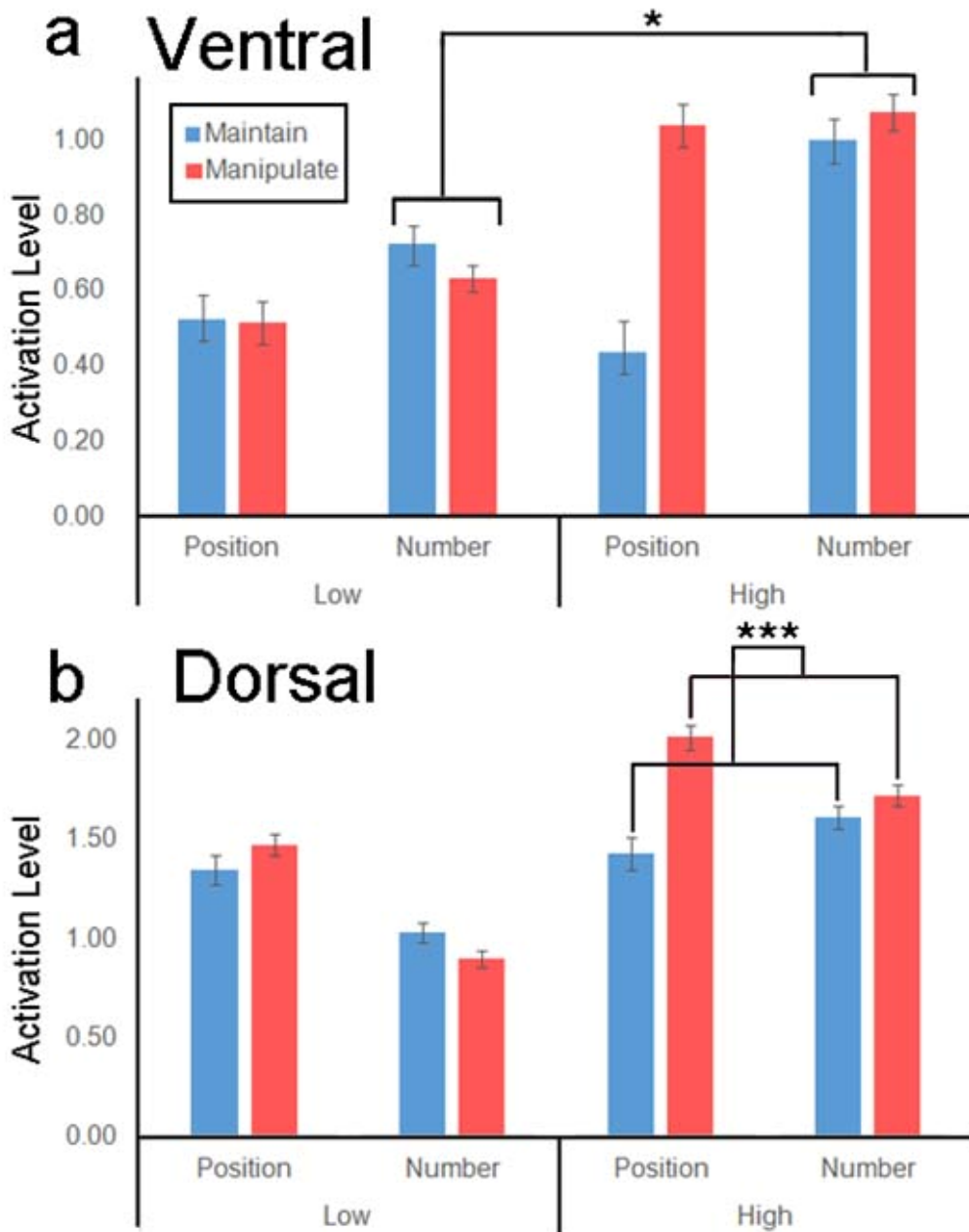


Figure 17: Significant interacting effects during the delay period of experiment 2.

(a) Beta-weights for ventral network. Findings demonstrate increased activation in the ventral network when required to process numbers at high load. (b) Beta-weights for dorsal network. Results revealed an increased activation in the dorsal network when required to manipulate at high load. ($*p < 0.05$, $**p < 0.01$, $***p < 0.001$) Error bars represent standard error of the mean.

1.15 Experiment 2: Whole brain analyses

Voxel-wise whole brain analyses were applied to test whether domain-specific effects from the first experiment could be replicated. Contrast maps comparing each of the experimental conditions to baseline were generated for individual participants and entered into a series of group-level random effects analyses. Data from the encoding and delay stage were analysed using a 2 x 2 x 2 factorial design with load, stimulus domain and type of cognitive process as factors. Unlike the first experiment, there was no need to use a conjunction analysis since there were only two levels for each of the factors.

Examination of the statistical parametric maps of stimulus-domain during the encoding stage (threshold corrected using FDR of $p < 0.05$) revealed that dorsal regions were sensitive for spatial processing whilst left-hemispheric regions were sensitive for number processing (Figure 18 and Table 3). A similar examination analysing the delay stage (threshold corrected using FDR of $p < 0.05$) revealed a similar dorsal and left-hemispheric activation for spatial and verbal processing respectively.

Examination of load effects during the encoding stage (threshold corrected using FDR of $p < 0.05$) showed that when contrasting high- against low-load trials, primary visual cortex and frontal brain regions were strongly activated (**Error! Reference source not found.**Table 3). Like the first experiment, contrasts that comparing high- and low-load trials during the delay stage showed no significant effect. No other significant main or interacting effects with domain were revealed.

Lastly, examinations of the cognitive process types showed no significant main or interacting effects during the encoding. As suspected, participants did not reveal any differences during encoding as they were unaware of whether to maintain or manipulate information. Similar contrasts (threshold corrected using FDR of $p < 0.05$) were used to examine the main and interacting effects during the delay stage. No main effects by cognitive process types were found. However, an interacting effect of load and cognitive process types (high against low load manipulation trials) revealed specific dorsal frontoparietal regions, very similar to the dorsal network of the MD areas, were recruited (Figure 19 and Table 3).

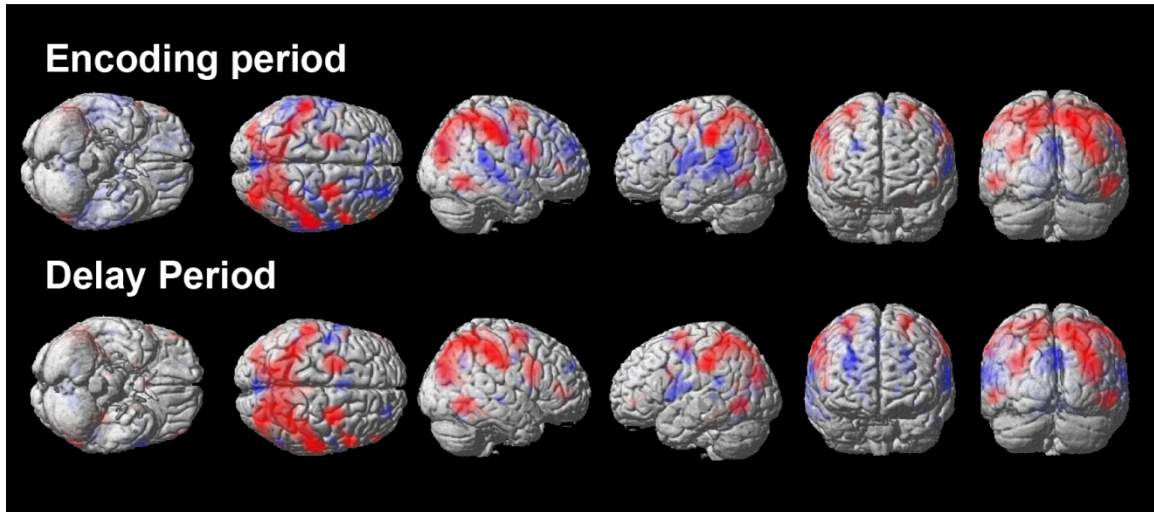


Figure 18: Whole-brain analyses from experiment 2. The figure depicts whole-brain maps from group-level analyses of experiment 2 with FDR correction at $p < 0.05$. Contrast activation of position against number trials during encoding and delay periods is shown in red. Similarly, contrast activation of number against position trials during encoding and delay period is shown in blue.

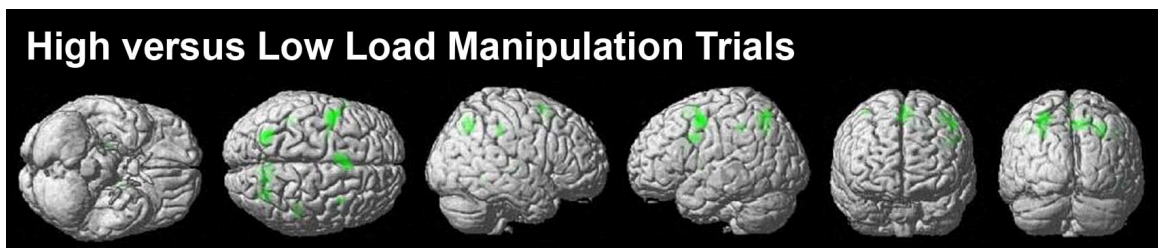


Figure 19: Whole-brain analysis of high versus low load manipulation trials. This figure depicts whole-brain maps from group analyses with FDR correction at $p < 0.05$.

Table 3: Peak activation coordinates from whole brain analysis of experiment 2.

Trial Type	x	y	z	t	Region	BA
Number (Verbal)	-51	-6	48	8.41	Post central gyrus	6
	-45	-42	21	7.28	L. Supplementary motor area	6
Encode Period	-21	-72	9	6.77	L. Calcarine	19
	30	-54	6	6.09	R. Calcarine	19
	-60	3	15	5.69	L. Rolandic Operculum	48
Position (Spatial)	39	-39	45	10.84	R. Inferior Parietal	40
	27	-3	60	8.82	R. Superior Frontal	6
Encode Period	-21	-3	57	8.02	L. Superior Frontal	6
	54	9	27	7.49	R. Inferior frontal operculum	44
	54	-57	-6	6.71	R. Inferior Temporal	37
	-54	-60	-6	5.42	L. Inferior Temporal	37
Load effects (High > Low)	-18	-72	-12	13.12	L Cerebellum	18
	-6	-78	-6	12.71	L. Lingual	17
Encode Period	6	-90	6	12.31	R Calcarine	17
	-51	-3	45	7.15	L Pre-central	6
	33	-3	54	5.50	R Mid Frontal	6
Number (Verbal)	-51	-6	48	7.09	Post central gyrus	6
	-3	6	63	5.99	L. Supplementary motor area	6
Delay Period	-45	-42	21	5.72	L. Supplementary Temporal	41
	-60	3	12	5.61	L. Rolandic Operculum	48
	-12	-78	15	5.21	Left Calcarine	17
	24	51	30	3.76	R. Middle Gyrus	46
Position (Spatial)	21	-63	57	11.89	R. Superior Parietal	7
	-18	-66	54	10.82	L. Superior Parietal	7
Delay Period	-24	-6	57	9.55	L. Superior Frontal	6
	30	-3	57	8.96	R. Superior Frontal	6
	54	9	30	6.86	R. Inferior frontal operculum	44
	-33	-39	-15	4.71	L. Fusiform	37
	54	42	6	4.03	R. Frontal Inferior Tri	45
Interacting effect (Load x Process)	-3	6	63	4.79	L Superior Motor Area	6
	-27	-63	54	4.60	L. Superior Parietal	7
High > Low	9	-66	48	4.40	R. Precuneus	7
	-48	0	51	4.32	L Precentral	6
	45	-33	36	4.07	-----	2

1.16 Discussion

The findings reported here demonstrate that the global, domain and process models are not mutually exclusive as was previously assumed. Instead, they provide different perspectives on the functional organisation of WM. For instance, results from the first experiment demonstrated that there was stimulus domain sensitivity across much of the frontoparietal cortices including the ventral MD network. In fact, the whole-brain analyses showed that dorsal, ventral and left-hemispheric frontoparietal cortices were differentially recruited when processing spatial, object and verbal stimuli respectively as described by the domain model. Critically, these sensitivities to stimulus domains were still evident when controlling for general difficulty. However, within MD cortex such differences were a matter of extent as opposed to absolute given that all MD sub-regions were still strongly activated during encoding and maintenance regardless of stimulus domains. Therefore, supporting evidence for both the domain and global models may be drawn from analysis of the same data.

Equally importantly, findings from our second experiment demonstrated that the process model also co-exists with the global model. Specifically, the ICA showed that two functional networks, ventral and dorsal, are encompassed within MD cortex. Like most WM experiments, both networks showed strong activation throughout the encoding and delay periods at all levels of load, for all stimulus domains and during both maintenance and manipulation. However, significantly greater activation was observed in the dorsal network when information had to be manipulated under high-load conditions whereas no such effect was evident in the ventral MD network.

The findings from these two experiments concur with our hypothesis that the global, process and domain models are not mutually exclusive. They also refined our hypothesis even further. Originally, we predicted that the process model provided a more detailed picture of the same system described by the global model given the results from our earlier study (Hampshire *et al.*, 2012). This prediction was true as sensitivities to cognitive processes differed across MD sub-networks whereby the dorsal network was significantly activated during manipulation demands. We also predicted that brain areas sensitive to stimulus domains would be orthogonal to the regions described by the global

and process models. However, this was not quite the case. Whilst many areas that showed domain sensitivity were located outside of the MD cortex, the ventral network was more active when processing object specific information even after accounting for general difficulty. Taken as a whole, the process model is nested within the global model whilst the domain model is partially overlapping. Despite this, all three models are partially correct at describing neural correlates of WM. As opposed to discrete processing modules, the data presented in this study can be best explained by functional gradients. It should be noted that gradients and networks may co-exist within a system.

Within the WM literature, many neuroimaging studies have poorly controlled visual display and motor response confounds that prevent a comprehensive analysis of WM activations. Generally, many neuroimaging studies focus on one stimulus domain, which does not allow for any isolation of stimulus-dependent dissociations and must be compared between experiments. To counter these issues, our WM paradigms displayed multiple stimulus domains simultaneously during the encoding and probe periods. In addition, participants had to select one of multiple post-delay changes depending on the cue presented at the beginning of the trial. As such, only the focus of attention and WM processes were manipulated. Given that only task-requirements were changing, our object-verbal-spatial dissociations did not fall prey to the same visual display confounds. In order to study the neural architecture during different cognitive processes, rotation and addition requirements were added into the delay period of our second WM experiment. This allowed for proper comparisons between different types of manipulation as well as stimulus domains. Furthermore, motor response confounds, including eye-movements, are rarely managed (Postle, 2006). Our paradigms required participants to make the same motor responses, such as eye movements, regardless of stimulus domains. By removing these confounds, our findings show a complete analysis of WM.

1.17 Independent buffers outside of MD

The global model postulates that MD regions are insensitive to stimulus features whilst adaptive to task specific information. Despite strong BOLD activity within MD regions throughout all stages of the WM tasks, only modest dissociations were observed within the ventral network during object specific trials. Furthermore, findings from the

whole-brain analyses revealed that caudal and posterior brain areas outside of MD cortex were variably recruited depending on the specific stimulus domain of focus. In detail, bilateral superior occipital and inferior parietal regions were activated during object WM; bilateral superior frontal sulci and superior parietal regions were recruited during spatial WM; and left lateral orbitofrontal and fronto-polar cortices were activated during verbal WM. This is very similar to the Multiple Component Model of WM, which defined WM as two stimulus-dependent independent buffers for storage and a stimulus-independent Central Executive System that organised information (Baddeley and Hitch, 1974). Our results suggest that the regions outside of MD parallel stimulus-dependent buffers whilst the regions inside MD resemble the stimulus-independent Central Executive System.

For WM tasks that use verbal stimuli, early research documented that Broca's area (area 44/45) was crucial for maintenance and sub-vocal rehearsal (Cohen *et al.*, 1997; Demb *et al.*, 1995; Awh *et al.*, 1996). Furthermore, patients with deficits in Broca's area have been documented to have aphasia. Conversely, prior research has demonstrated that the posterior part of the superior frontal sulcus is significantly activated by WM tasks that use spatial stimuli (Courtney *et al.*, 1998). Disturbances within this area following stroke (Carlesimo *et al.*, 2001) or trans-cranial magnetic stimulation (Mottaghy *et al.*, 2002) selectively interfere with spatial processing. In contrast, WM tasks that use object stimuli have been documented to activate the ventral PFC including inferior and middle frontal gyri (Courtney *et al.*, 1996; Courtney *et al.*, 1997). Disruption of the ventral PFC has been documented to show selective impairment on non-spatial WM tasks (Bechara *et al.*, 1998; Mottaghy *et al.*, 2002). Within our experiments, an assortment of brain regions including Broca's area was recruited when participants focused on verbal information. In contrast, the superior frontal gyrus and dorsal parietal areas were recruited when participants attended to spatial stimuli. Conversely, many ventral frontoparietal areas including ventral MD regions were recruited when focusing on fractal objects. In summary, results from our experiments and literature review have shown that dorsal, ventral and left-hemispheric frontoparietal areas outside of stimulus-independent MD regions are variably recruited for verbal, spatial and non-spatial processing depending on task requirements.

Unlike spatial and verbal processing, object stimuli have inherent spatial and non-spatial characteristics including texture, colour and orientation (Courtney, 2004). Furthermore, participants have been known to verbalise objects in order to improve encoding. As such, isolating brain regions specific for non-spatial processing is rather difficult. Within our own study, we used fractal patterns as objects in order to prevent participants from verbalising the stimuli. However, these abstract fractals were inherently more difficult compared to verbal and spatial stimuli and also contained higher-order structure, which may be more salient to lateral frontal cortices (Bor *et al.*, 2003). For future studies, using less complex object specific stimuli may be more appropriate when identifying non-spatial stimulus specific brain areas.

1.18 Adaptive coding and specialisation

The global model proposes that WM, attention and cognitive control are all subsets of a common underlying cognitive process due to the highly adaptable nature of the MD regions. From a detailed perspective, neurons within MD have adaptive coding properties that process task-relevant information, thus generating a temporary mental workspace. Moreover, these neurons are involved in almost all tasks with nominal functional specialisation (Duncan, 2001; Duncan 2006). However, specialisation within MD regions is not necessarily exclusive with the idea of an adaptive coding system. For example, some ventral MD regions may house neurons that adapt to code for simple and concrete aspects of a task such as relevant stimuli and planned responses (Hampshire *et al.*, 2009). Other more dorsal regions may adapt to code for task relevant rules and higher order relationships between maintained items (Hampshire & Owen, 2010). To put it another way, there may be subdivisions between regions that simply hold representations online and regions that process those representations by rearranging or chunking them in order to predict outcomes and solve problems. Consequently, the same subdivisions posited by the process model may actually be nested within the global model.

Indeed, our results revealed that two functionally distinct networks exist within the MD regions and are co-recruited during the encoding and delay periods of WM tasks. In both experiments, a ventral network composed of the AI/FO and SMA/ACC, and a dorsal network composed of the right IFS and bilateral IPS were consistently extracted.

These two components, which explained the most variance in MD cortex, are very similar to the networks reported in our previous study (Hampshire *et al.*, 2012) and roughly indistinguishable in the two experiments reported here (Figure 155) although the dorsal network is stronger in second task. More importantly, these two networks are strikingly similar to the ventral-dorsal functional axis of the process model. This model proposes that the VLPFC subserves simple cognitive operations such as active selection and comparisons, whilst the DLPFC subserves higher-order executive processes including manipulating information (Petrides, 1994; Owen *et al.*, 1998). In the previous study (Hampshire *et al.*, 2012), tasks that required short-term memory maintenance strongly activated the ventral network, whilst tasks that required mental manipulation strongly activated the dorsal network. In this study, findings from our experiments revealed that only the dorsal network is more activated when manipulating information at high loads.

The dorsal network has been activated by a host of psychological tasks including chunking (Bor *et al.*, 2003), analogical reasoning (Hampshire *et al.*, 2011) spatial planning (Cohen *et al.*, 1996), mental rotation (Owen *et al.*, 1996) and arithmetic. Our results showed that this network was recruited during addition and spatial rotation with no particular sensitivity for either process. In addition, the dorsal network showed increased BOLD signal during the encoding period of high-load trials for both experiments. In line with prior research (Postle *et al.*, 1999; Rympha *et al.*, 1999; Bor *et al.*, 2003), this network is likely recruited to chunk information in order to improve encoding. Originally, we expected that the dorsal network would also be recruited when manipulating information at low loads. However, some participants may have both encoded and transformed the stimuli during the encoding period in order to find the unmatched target more accurately. If true, the dorsal network may have been less activated during the delay period of manipulation trials. In contrast, participants may not have processed and held both encoded and transformed information during higher loads. Additional experiments are needed to verify this claim. On a more general role, the dorsal network has been proposed to be a specialised hub for transforming information according to task rules (Hampshire & Owen, 2010).

The ventral network has been activated by a host of tasks including inhibition (Hampshire *et al.*, 2010), target detection (Hampshire *et al.*, 2009), and extra-dimensional shifting (Hampshire *et al.*, 2006) among many others. Our first experiment revealed that though the ventral network was activated by all stimulus domains, objects showed greater activation during the encoding and delay. As a result, it is possible that this network carries a greater sensitivity for non-spatial information, but given that spatial and verbal stimuli also activated this network, it is rather unlikely. Instead, it is possible that processing certain stimuli such as fractals required more attention than processing spatial and verbal stimuli. On a general level, the ventral network has been proposed to maintain and bias attention between competing representations in modality specific posterior regions in order to maintain their relevance to current behavioural goal (Owen and Hampshire, 2009).

1.19 Recent Meta-analysis

Observations in a recent meta-analysis (Rottschy *et al.*, 2012), which included 189 fMRI experiments, accorded well with our results. First, the analysis revealed a stimulus-general central core network engaged in many WM tasks. The same authors also suggested that this network may not be limited to WM but may also span several higher cognitive functions, including attention and action control. Second, their results showed that n-back tasks, which generally place greater demands on manipulation, converged in the DLPFC. In contrast, Sternberg tasks, which normally place greater demands on maintenance, showed more consistent activation in the left inferior frontal gyrus. Critically, this would mean that the ventral-dorsal functional axis of the process model exists in the LPFC. Lastly, their analysis demonstrated ventral and dorsal brain regions specific for non-spatial and spatial stimuli respectively in more posterior and caudal areas of the frontal lobe. Similar to our results, their core WM network is both anatomically and functionally similar to the MD regions of the global model. Furthermore, their results also showed that activation differences from the n-back and Sternberg tasks parallel the ventral-dorsal functional axis posited by the process model. In addition, their stimulus specific dissociation showed similar posterior ventral and dorsal dissociations for non-

spatial and spatial stimuli respectively. When collapsing over one hundred WM experiments, their results show many similarities with our observations.

1.20 Conclusion

A consensus has not yet been reached regarding the functional organisation of WM processes within the brain, but our experiments here have the potential to reconcile the domain, process and global models. Critically, our results show that these models are not mutually exclusive and all three models may in fact be partially correct. The process model is nested within the MD regions of the global model, whilst the domain model is partially independent from the others. On a very broad level, many cognitive functions including WM, attention and cognitive control rely heavily on the adaptive coding properties of the frontoparietal MD cortex (Duncan 2006). However, this does not exclude the possibility of specialisation, as previous research has demonstrated that a ventral/dorsal functional axis exists within these regions (Hampshire *et al.*, 2012). Our results further demonstrate that this axis is comparable to the axis of the process model whereby the ventral and dorsal networks are activated by maintenance and manipulation respectively. Beyond the general global processing of MD regions, WM also requires specialised buffers located in other brain regions. Our results demonstrated that dorsal, ventral and language regions outside of MD are recruited during spatial, non-spatial and verbal processing respectively. In conclusion, our results support the theory that WM is an emergent property of multiple specialised brain systems, and the three views discussed here are not mutually exclusive and paint a more comprehensive picture of WM.

References or Bibliography

- Awh, E., Jonides, J., Smith, E. E., Schumacher, E. H., Koeppel, R. A., & Katz, S. (1996). Dissociation of storage and rehearsal in verbal working memory: Evidence from positron emission tomography. *Psychological Science*, 25-31.
- Baddeley, A. D., & Hitch, G. J. (1974). Working memory. *The psychology of learning and motivation*, 8, 47-89.
- Baddeley, A., Logie, R., Bressi, S., Sala, S. D., & Spinnler, H. (1986). Dementia and working memory. *The Quarterly Journal of Experimental Psychology*, 38(4), 603-618.
- Bechara, A., Damasio, H., Tranel, D., & Anderson, S. W. (1998). Dissociation of working memory from decision making within the human prefrontal cortex. *The journal of neuroscience*, 18(1), 428-437.
- Bor, D., Duncan, J., Wiseman, R. J., & Owen, A. M. (2003). Encoding strategies dissociate prefrontal activity from working memory demand. *Neuron*, 37(2), 361-367.
- Carlesimo, G. A., Perri, R., Turriziani, P., Tomaiuolo, F., & Caltagirone, C. (2001). Remembering what but not where: independence of spatial and visual working memory in the human brain. *Cortex*, 37(4), 519-534.
- Cohen, M. S., Kosslyn, S. M., Breiter, H. C., DiGirolamo, G. J., Thompson, W. L., Anderson, A. K., ... & Belliveau, J. W. (1996). Changes in cortical activity during mental rotation A mapping study using functional MRI. *Brain*, 119(1), 89-100.
- Cohen, J. D., Perlstein, W. M., Braver, T. S., Nystrom, L. E., Noll, D. C., Jonides, J., & Smith, E. E. (1997). Temporal dynamics of brain activation during a working memory task.
- Courtney, S. M. (2004). Attention and cognitive control as emergent properties of information representation in working memory. *Cognitive, Affective, & Behavioral Neuroscience*, 4(4), 501-516.
- Courtney, S. M., Ungerleider, L. G., Keil, K., & Haxby, J. V. (1997). Transient and sustained activity in a distributed neural system for human working memory. *Nature*, 386(6625), 608-611.
- Courtney, S. M., Petit, L., Maisog, J. M., Ungerleider, L. G., & Haxby, J. V. (1998). An area specialized for spatial working memory in human frontal cortex. *Science*, 279(5355), 1347-1351.
- Demb, J. B., Desmond, J. E., Wagner, A. D., Vaidya, C. J., Glover, G. H., & Gabrieli, J. D. (1995). Semantic encoding and retrieval in the left inferior prefrontal cortex: a functional MRI study of task difficulty and process specificity. *Journal of Neuroscience*, 15(9), 5870-5878.
- D'Esposito, M., Postle, B. R., & Rypma, B. (2000). Prefrontal cortical contributions to working memory: evidence from event-related fMRI studies. *Experimental Brain Research*, 133(1), 3-11.

- Duncan, J. (2001). An adaptive coding model of neural function in prefrontal cortex. *Nature Reviews Neuroscience*, 2(11), 820-829.
- Duncan, J. (2006). EPS Mid-Career Award 2004: brain mechanisms of attention. *The Quarterly Journal of Experimental Psychology*, 59(1), 2-27.
- Duncan, J., & Owen, A. M. (2000). Common regions of the human frontal lobe recruited by diverse cognitive demands. *Trends in neurosciences*.
- Gray, J. R., Chabris, C. F., & Braver, T. S. (2003). Neural mechanisms of general fluid intelligence. *Nature neuroscience*, 6(3), 316-322.
- Jonides, J. (1995). Working memory and thinking. *Thinking: An invitation to cognitive science*, 3, 215-265.
- Hampshire, A., Chamberlain, S. R., Monti, M. M., Duncan, J., & Owen, A. M. (2010). The role of the right inferior frontal gyrus: inhibition and attentional control. *Neuroimage*, 50(3), 1313-1319.
- Hampshire, A., Highfield, R. R., Parkin, B. L., & Owen, A. M. (2012). Fractionating human intelligence. *Neuron*, 76(6), 1225-1237.
- Hampshire, A., & Owen, A. M. (2006). Fractionating attentional control using event-related fMRI. *Cerebral Cortex*, 16(12), 1679-1689.
- Hampshire, A., & Owen, A. M. (2010). Clinical studies of attention and learning. *Attention and Associative Learning: From Brain to Behaviour*, 385.
- Hampshire, A., Thompson, R., Duncan, J., & Owen, A. M. (2009). Selective tuning of the right inferior frontal gyrus during target detection. *Cognitive, Affective, & Behavioral Neuroscience*, 9(1), 103-112.
- Hampshire, A., Thompson, R., Duncan, J., & Owen, A. M. (2011). Lateral prefrontal cortex subregions make dissociable contributions during fluid reasoning. *Cerebral Cortex*, 21(1), 1-10.
- Levy, R., & Goldman-Rakic, P. S. (2000). Segregation of working memory functions within the dorsolateral prefrontal cortex. In *Executive Control and the Frontal Lobe: Current Issues* (pp. 23-32). Springer Berlin Heidelberg
- Miller EK and Cohen JD (2001). An integrative theory of prefrontal cortex function. *Annual Review of Neuroscience*. 24: 167-202.
- Mottaghy, F. M., Keller, C. E., Gangitano, M., Ly, J., Thall, M., Parker, J. A., & Pascual-Leone, A. (2002). Correlation of cerebral blood flow and treatment effects of repetitive transcranial magnetic stimulation in depressed patients. *Psychiatry Research: Neuroimaging*, 115(1), 1-14.
- Owen AM, Evans AC and Petrides M (1996). Evidence for a two-stage model of spatial WM processing within the lateral frontal cortex: a PET study. *Cerebral Cortex*. 6: 31-38.
- Owen, A. M., Stern, C. E., Look, R. B., Tracey, I., Rosen, B. R., & Petrides, M. (1998). Functional organization of spatial and nonspatial working memory processing

- within the human lateral frontal cortex. *Proceedings of the National Academy of Sciences*, 95(13), 7721-7726.
- Petrides, M. (1991). Functional specialization within the dorsolateral frontal cortex for serial order memory. *Proceedings of the Royal Society of London. Series B: Biological Sciences*, 246(1317), 299-306.
- Petrides, M. (1994). Frontal lobes and behaviour. *Current opinion in neurobiology*, 4(2), 207-211.
- Petrides, M. (1995). Impairments on nonspatial self-ordered and externally ordered working memory tasks after lesions of the mid-dorsal part of the lateral frontal cortex in the monkey. *The Journal of Neuroscience*, 15(1), 359-375.
- Postle, B. R. (2006). Working memory as an emergent property of the mind and brain. *Neuroscience*, 139(1), 23-38.
- Postle, B. R., Berger, J. S., & D'Esposito, M. (1999). Functional neuroanatomical double dissociation of mnemonic and executive control processes contributing to working memory performance. *Proceedings of the National Academy of Sciences*, 96(22), 12959-12964.
- Rottschy, C., Langner, R., Dogan, I., Reetz, K., Laird, A. R., Schulz, J. B., ... & Eickhoff, S. B. (2012). Modelling neural correlates of working memory: a coordinate-based meta-analysis. *Neuroimage*, 60(1), 830-846.
- Rympa, B., Prabhakaran, V., Desmond, J. E., Glover, G. H., & Gabrieli, J. D. (1999). Load-dependent roles of frontal brain regions in the maintenance of working memory. *Neuroimage*, 9(2), 216-226.
- Ungerleider, L. G., & Haxby, J. V. (1994). 'What' and 'where' in the human brain. *Current opinion in neurobiology*, 4(2), 157-165.
- Woolgar, A., Parr, A., Cusack, R., Thompson, R., Nimmo-Smith, I., Torralva, T., & Duncan, J. (2010). Fluid intelligence loss linked to restricted regions of damage within frontal and parietal cortex. *Proceedings of the National Academy of Sciences*, 107(33), 14899-14902.

Jeffrey Penn Wong

EDUCATION

Candidate for Master of Science in Neuroscience- University of Western Ontario **2014**

- Awarded the Queen Elizabeth II graduate scholarship in Science and Technology
- Awarded Western Graduate scholarship
- Teaching Assistant for Psychology 1000

Bachelor of Medical Science - University of Western Ontario **2011**

- Honours Specialization in Physiology (Western Scholar)
- Recipient of Queen Elizabeth II Aiming for the Top Scholarship (2007-2011)
- Dean's Honour list (2007-2011)

ACADEMIC RESEARCH

Master's Thesis **2014**

Graduate student to Dr. Adrian Owen and Dr. Adam Hampshire (Brain and Mind Institute)

- Programmed a novel working memory paradigm that demonstrates functionally dissociation between executive functions and mnemonic processes within the prefrontal lateral cortex
- Gained proficiency in neuroimaging software (MATLAB, SPM, GIFT, MarsBar), statistical packages (SPSS, R) and UNIX/Linux operating system

Honour's Thesis **2011**

Fourth year student to Dr. Brian Corneil (Brain and Mind Institute)

- Collected and analysed intramuscular EMG recordings of neck splenius capitis muscle in humans to assess the empirical measure of the stop signal reaction time
- Learned to generate MATLAB scripts, analyse EMG and EOG recordings and gained proficiency programming using MATLAB

RELATED WORK EXPERIENCE

Programmer for Cambridge Brain Sciences Inc. **Ongoing**

- Designed multiple neurocognitive paradigms for internet-based studies including: Reversal learning, Iowa gambling, Digit-span, Analogical reasoning and many others

COMMUNITY INVOLVEMENT

Research assistant for Geriatric neuroimaging study **Ongoing**

- Screened patients with mild cognitive disorder for fMRI experiments, administered cognitive tests of executive functions, and analysed/interpreted data detailing functional changes pre- and post- intervention

PUBLICATIONS

Goonetilleke, S.C., **Wong, J.P.**, Corneil, B.D. (2012) Validation of a within-trial measure of the oculomotor stop process. *J. Neurophys.* 108: 760-770