Neural Activity Associated with the Processing of Familiar Information in Working Memory

by

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Abstract

Purpose: Emerging data indicate that processing of familiar and novel faces involves different neural mechanisms; familiar face perception is associated with more widespread neural activity in prefrontal and temporal regions compared with novel faces (Leveroni et al., 2000). Nevertheless, investigation of working memory in the context of personally significant information is limited.

Method: Sixteen healthy individuals performed *n*-back tasks while undergoing functional magnetic resonance imaging at the University of Alberta. A yoked design was used to pair familiar faces (family members / close friends) with novel faces across participants (Roye, Schroger, Jacobsen, & Gruber, 2010). Participants compared the current face with the one before (1-back) or two faces before (2-back). There were 6 runs, each consisting 6 blocks of 1-back and 2-back conditions. Statistical parametric mapping (SPM) 8 was used for statistical analysis.

Results: Hit rates were comparable between 1-back and 2-back conditions for familiar faces (93.7% and 89.1% respectively; $p>0.05$) but were slightly higher in 1-back than 2-back conditions for novel faces (89.1% and 82.7% respectively, $p<0.05$). In the 1-back condition, familiar faces demonstrated substantial activations in prefrontal, occipital, and cerebellar regions compared with novel faces. In the 2-back condition, both familiar and novel faces activated the typical frontoparietal working memory network; however, novel faces activated more extensively and also activated the insula and thalamus, whereas familiar faces activated less extensively and also activated the cerebellum. In addition, the main effect of familiarity and pair-wise comparison of familiar versus novel faces on the 2-back condition showed strong neural activity in the anterior

cingulate cortex. Region of interest (ROI) analysis revealed dissociable pattern of brain-behavior relationship: Neural activity for familiar 2-back condition showed positive correlation with hit rate and negative correlation with reaction time over many regions such as the superior and medial frontal gyrus, the occipital cortex, and the anterior cingulate cortex, while neural activity for novel 2-back condition showed negative correlation with hit rate and positive correlation with reaction time at the medial frontal gyrus. This further suggests that familiar information, relative to novel information, has a facilitative effect on working memory.

Conclusions: Familiar and novel faces demonstrated different patterns of activation in working memory tasks. Although both conditions activated the typical working memory network, familiar faces demonstrated fewer actiavtions than novel faces in the 2-back condition, suggesting that working memory on familiar faces requires less effort. In addition, the neural activity associated with the processing of familiar faces also demonstrated a pattern of facilitation, with greater neural activity related to higher accuracy rate and lower reaction time on task; such pattern was absent for novel faces. From the results of the 1-back condition, the processing of familiar faces appeared to elicit more extensive activations, consistent with previous findings that more widespread neural changes in familiar face perception. The results suggest a differential use of personally significant information in face perception and working memory training.

Preface

This thesis is an original work by Benson Ng. The research project, of which this thesis is a part, received research ethics approval from the University of Alberta Research Ethics Board, Project Name “Neural basis of auditory working memory and executive function”, No. Pro00027867, from February 13, 2012, to July 23, 2018.

Dedication

This thesis is dedicated to my parents, Tony and Rosa, as well as my brother, Jason, for their continuous support and encouragement throughout my years of study. This accomplishment would not have been possible without them. Thank you.

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Benson Ng

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List of Abbreviations

fMRI	Functional Magnetic Resonance Imaging
MRI	Magnetic Resonance Imaging
BA	Brodmann Area
PET	Positron Emission Tomography
SPM	Statistical Parametric Mapping
ACC	Anterior Cingulate Cortex
PCC	Posterior Cingulate Cortex
FG	Fusiform Gyrus
FFA	Fusiform Face Area
ROI	Region of Interest
ANOVA	Analysis of Variance
F1	Familiar 1-back
F2	Familiar 2-back
N1	Novel 1-back
N2	Novel 2-back

Chapter 1 Literature Review

Introduction

Memory has always been the center of research for decades. Many individuals with neurological (e.g., Alzheimer's disease, epilepsy, Parkinson's disease) or psychiatric (e.g., schizophrenia, post-traumatic stress disorder) disorders often report a degree of impairment in memory (McKhann et al., 1984; Green, 1996). Therefore, there has been much research dedicated to understanding the underlying mechanisms of memory. The purpose of past studies is to derive effective cognitive training strategies for improving memory and other related executive functions (Heinzel et al., 2014; Penner et al., 2012). Nevertheless, there is still uncertainty on the parameters for training, e.g., the nature of stimuli used in training for inducing neuroplasticity, the duration of training, and the types of cognitive training (von Bastian & Oberauer, 2013). Moreover, most of the previous studies on working memory processing were conducted using abstract stimuli such as figures, patterns, tones, numbers, or letters. There are limited working memory studies that used stimuli that had a significant personal attachment to the individual. Using significant personal information could provide a more comprehensive understanding of human working memory processing and explore the possibility of using personal significant stimuli in cognitive training. The present study takes the initiative to examine the neural processing of working memory using personally significant information as stimuli. The aims are three folds: First, it would allow us to understand the differences of neural mechanism in processing novel/ abstract information (as it used to be in most existing memory processing and training paradigms) and personally significant information. Second, it would serve to help identify neural regions that may take a pivotal role in diverting information during working memory processing. Third, it would help delineate the use of different nature of stimuli for inducing desired neural activity.

Memory

Long-term, Short-term, and Working Memory

Memory is generally classified as short-term or long-term. Short-term memory refers to the ability to hold a limited amount of information for several seconds or minutes (Cowan, 2008), such information will decay over time due to the constant update of new information. Long-term memory refers to the ability to store a variety of knowledge and events without any capacity limitation, such information can be retrieved at any time and more resistant to forgetting (Cowan, 2008).

The term working memory has been used interchangeably with short-term memory in literature, however, it remains controversial whether they are conceptually the same and reflect identical cognitive functions. Some believe that the two are the same construct due to extensive overlapping between them, others have a different opinion (Aben, Stapert, & Blokland, 2012). In this thesis, working memory is defined as a type of executive function with limited capacity that is responsible for holding, processing, and manipulation of information for a short period of time (Baddeley, 1986, 1992). Performing simple mathematic calculations in our heads is a prime example of working memory in use, as it requires a short-term capacity of remembering the numbers and performing calculations.

Previous research tried to understand the mechanism of working memory had proposed several working memory models. One of the most influential working memory models is Baddeley and Hitch's multi-component model (1974). According to the model, a central executive with a limited attentional capacity of information storage and manipulation acts as a control system for the three subcomponents of working memory: phonological loop, visuospatial sketchpad, and episodic buffer (Repovs & Baddeley, 2006). Phonological loop provides a limited capacity for the

storage and maintenance of verbal information which is then temporarily stored in phonological or acoustic form prior to repeated articulation in order to revive memory trace for storage and later retrieval. Another distinct subcomponent of the multi-component model is the visuospatial sketchpad, which is specialized for maintaining and manipulating visual and spatial information. The episodic buffer is the latest subcomponent added to be part of the multi-component model (Baddeley, 2000). This buffer serves as a separate storage to integrate information from different modalities, including phonological loop and visuospatial sketchpad, as well as other elements of memory (short-term and long-term) to form complex, comprehensive structures (Repovs & Baddley, 2006).

Variation of Working Memory Paradigms

Researchers have developed several cognitive tasks which allow the engagement of temporarily storing and manipulation of information; these include the digit span task (Lefebvre, Marchand, Eskes, & Connolly, 2005), Sternberg recognition task (Jensen & Lisman, 1998), delay-to-match-sample task (Moody, Wise, di Pellegrino, & Zipser, 1998), and the n-back task (Owen, McMillian, Laird, & Bullmore, 2005). The digit span task requires participants to repeat a string of digits in the forward or reverse order (backward) that are sequentially presented to them. Working memory capacity is estimated from the number of digits that can be correctly recalled. In the Sternberg recognition task, participants viewed a set of stimuli followed by a delay to maintain information 'online', the stimuli are then later tested by a probe stimulus to determine whether or not it is part of the set. The delay-match-to-sample task requires participants to remember a stimulus and identify from a subsequent set of stimuli following a delay. The n-back task consists of a series of stimuli are presented in quick succession, and participants are required to compare current stimulus with n trials before.

Although the shared theme is to assess the function of working memory, variations exist among these tasks regarding content, stimulus modality (verbal/ visual), duration of delay or interference, and cognitive load demands. It is thus essential to use appropriate paradigms, and design stimuli that fit best to the proposed research question. In the present study, we intend to investigate the effect of facial familiarity in working memory among healthy adults. The task must not only be capable of presenting of familiar and novel faces but also be able to have different cognitive loads in order to investigate the relationship of working memory load and familiarity effect. Based on the above criteria, the n-back paradigm is chosen to be the paradigm used in the present study.

N-back Task

N-back task is a cognitive task that is commonly used to assess the performance of working memory capacity and taps heavily into the maintenance and manipulation process (Beneventi, Barndon, Ersland, & Hugdahl, 2007). The task was first developed and introduced by Wayne Kirchner in 1958, with an aim to explore age differences in terms of memory by measuring short-term retention among young and older adults. The n-back task was then adopted and has been widely used in the field of cognitive science as a valid and reliable assessment tool for working memory.

Although many variations of stimuli exist in the n-back task, the concept of n-back remains the same across studies. Stimuli are presented in quick succession one-by-one, participants are required to decide whether the current stimulus matches the one presented n trials prior, where n can be 1, 2, 3 and so on. For example, during 1-back condition, participants would treat a target as the match between the current stimulus and the stimulus immediate before. In a 2-back condition, participants would need to compare the current stimulus with the stimulus presented two trials

prior. As the number gets higher, the task becomes more difficult as it requires more cognitive demand to process more stimuli simultaneously. A majority of neuroimaging studies have used 1-back and 2-back tasks as 3-back or more are too mentally demanding and might reduce the reliability of results (von Bastian & Oberauer, 2013).

N-back tasks using visual or verbal stimuli are popular tasks for assessing the processing of visual and verbal information in working memory, respectively. For example, visual information can be assessed by presenting photos of visuospatial objects, faces, scenes to elicit visual and emotional processing areas, while verbal information can be assessed by presenting digits, letters, words to activate different brain regions responsible for phonological processing while performing a working memory task. Some studies even combine the processing of visual and verbal information in one n-back paradigm, forming a dual n-back task (Lilienthal, Tamez, Shelton, Myerson, & Hale, 2013; Salminen, Kuhn, Frensch, & Schubert, 2016).

Neural Mechanism of Working Memory

Neuroimaging studies have demonstrated that working memory consists of a set of brain regions that is commonly referred as the frontoparietal neural network, including the frontal and parietal lobes, thalamus, and anterior cingulate cortex (ACC) (Owen et al., 2005). However, specific brain regions are activated in response to certain stimuli and tasks, producing different patterns of neural activation in working memory. For example, tasks with figures activate the precuneus and inferior parietal lobe (Owen et al., 2005), auditory stimuli activate the superior temporal and inferior parietal lobe (Alain, Arnott, Hevenor, Graham, & Grady, 2001), and visuospatial images activate specific parts of the prefrontal lobe and posterior parietal lobe (Carlson et al., 1998).

Neural Mechanism of Working Memory – Familiarity Factor

Hasselmo and Stern (2006) reviewed the neural mechanisms underlying working memory for novel and familiar information by evaluating existing lesion, neurophysiology and neuroimaging studies. They found supporting evidence that working memory for novel and familiar information engage in slightly different neural mechanisms: novel stimuli require substantial acetylcholinergic activations in the entorhinal and parahippocampal regions in addition to the frontoparietal network which is already sufficient to maintain working memory functioning for familiar stimuli.

Using the n-back task, a functional magnetic resonance imaging (fMRI) study by Stern, Sherman, Kirchhoff, & Hasselmo (2001) investigated the contributions of medial temporal and prefrontal cortices to working memory tasks with familiar and novel stimuli. Participants were shown photos of indoor and outdoor scenes. Familiar stimuli referred to one set of photos that were presented 14 times for participants to get familiarized with the stimuli prior to scanning. Novel stimuli referred to the set of photos that participants were never exposed to. They found shared activations within the prefrontal and parietal cortices in the 2-back condition among familiar and novel stimuli. However, greater signal changes in parahippocampus were demonstrated in addition to frontoparietal activations among novel stimuli.

Similar event-related fMRI studies also demonstrated parahippocampal activations related to novel face stimuli in working memory (Ranganath & D'Esposito, 2001; Ranganath & Rainer, 2003). Ranganath and D'Esposito (2001) assessed the role of medial temporal lobe during encoding, maintenance, and retrieval of familiar and novel faces during a delayed-recognition working memory task. Their fMRI results revealed bilateral activations in the anterior hippocampus during the delayed period; parahippocampal gyrus demonstrated sustained

activations during encoding and retrieval phase in working memory task. When comparing the familiarity of information, these two regions elicited greater activations in novel face condition than in familiar face condition.

Beneventi and colleagues (2007) investigated working memory using schematic drawings of facial expressions. A distributed bilateral activation was found in response to increasing working memory load; specific regions include inferior parietal lobule, dorsolateral prefrontal cortex, supplementary motor area, and the cerebellum. Right inferior frontal gyrus was activated in favor of facial drawings.

Processing personally significant information - Faces

The brain undergoes tremendous development since conception, and continues throughout childhood, adolescence, and even early adulthood in some parts of the brain. Basic sensory functions (e.g., five senses) and motor functions are established at the early stage of childhood. However, other complex functions including language production and comprehension, reasoning, and abstract thinking do not develop till a later stage of life.

As important as fundamental sensory and motor functions, the ability to recognize faces has been an essential function for human beings. For example, infants and children recognize their parents' faces in search of food, comfort, and safety, while children, teens, and adults can quickly identify their close friends and families, partners, colleagues, and adjust their social behaviors accordingly. As such, it is no surprise that the capability to recognize a face is innate. It has been shown that infants have the ability to discriminate human faces among other animal faces and non-living objects, and infants develop preferences towards human faces or face-like stimuli as early as their first year (Frank, Vul, & Johnson, 2009).

Many previous studies have been dedicated to understanding the process of face recognition in human beings. Although various models attempted to explain face recognition, the majority do not seem to explain the entire phenomenon. Until now, there is much debate regarding models and theories underlying the neural systems for face perception. Some proposed the existence of a brain region that is specialized for face perception (e.g., Bruce and Young's Model), while others believed face perception is achieved by a distributed neural network (e.g., Haxby's Distributed Model).

Bruce and Young's Model

Bruce and Young's (1986) model is one of the most widely accepted models for face recognition. They proposed that identifying faces involves a series of stages that occur sequentially. In the first stage of the model, which is called structural encoding, the individual builds a fundamental representation of the face by compiling rudimentary facial information (e.g., individual features and expression). Following structural encoding is two independent but parallel routes: one is responsible for face and person recognition and the other for visual operations such as expression analysis (comprehension of emotional state), facial speech analysis (speech perception from processing lip and facial movement), and directed visual processing (search of specific features to aid face recognition) (Dubois et al., 1998). The information is then directed to the cognitive system where incoming facial information is quickly compared with the stored information followed by the generation of biographical information (e.g., names, occupations).

Bruce and Young's model specified the dissociation between identity representation and other features of human faces, including affective expressions (Winston, Henson, Fine-Goulden, & Dolan, 2004). This model also explained why recognition is easier than identifying a familiar person, as well as the tip-of-the-tongue phenomenon. According to this model, successful name

recall is difficult to achieve because it requires successful processing of the previous stages (Werheid & Clare, 2007).

Haxby's Distributed Model of Face Perception

Different from Bruce and Young's model, Haxby, Hoffman, & Gobbini (2000) believed that face perception is mediated by distributed processing. They proposed that face processing can be mediated by a distributed neural network based on two dissociable processing: invariant and changeable features of faces (e.g., expression and eye gaze). According to this model, visual analysis of faces is achieved by activating the core regions, which consists of the fusiform face area, inferior occipital gyrus - occipital face area, and posterior superior temporal sulcus. These regions respond more strongly when viewing faces relative to other objects, and hence constituted the core regions for visual analysis of faces. Although bilateral activations can be found within these core regions, right lateralized activations are reported to be larger and more consistent (Haxby & Gobbini, 2010).

Besides the core regions, an "extended system" which refers to adjacent cortices, including the frontal lobe, limbic system, amygdala, anterior temporal cortex, also facilitates face processing by extracting various types of information from faces (Werheid & Clare, 2007; Liu et al., 2013; Haxby & Gobbini, 2010). Overall, face processing operates in a hierarchical manner; the core system receives fundamental visual information before exerting influence on the extended system for further face processing (Liu et al., 2013).

Concept of Familiarity – Novel versus Familiar Face Processing

Definition of familiar faces can vary between studies. Some might refer to famous faces such as celebrities or anyone who is frequently exposed in media, others might refer familiarity to a feeling of "previously seen" even when these faces are not considered as public figures (Dubois

et al., 1998). Faces of famous people typically activate semantic knowledge only due to a lack of direct social interaction or relevance with normal individuals (Sugiura, 2014). Recent studies confirmed the notion that differences lied between familiar and novel face recognition. Familiar faces can be recognized even in an impoverished condition, while novel face perception is greatly influenced by varying lightings, viewpoint, or expression (Hancock, Bruce, & Burton, 2000). Also, change in external features such as hairstyle or facial hair can affect novel face recognition performance, whereas recognition of familiar face relies more on internal features, including eyes, nose, and mouth (Young, Newcombe, de Hann, Small, & Hay, 1993). Although the definition of familiar faces can vary, one thing that can be certain is that familiar and novel face perception differs in a significant way.

Processing of Faces of Personally Significant Individuals

According to Haxby and Gobbini (2010), one of the key components of familiar face recognition is the ability to immediately retrieve information about the familiar individuals, also known as the retrieval of personal knowledge. Upon identifying a face, especially a familiar face, we tend to adjust our social behavior more appropriately based on previous encounters and knowledge of that individual. According to Sugiura (2014), personally significant/familiar people consist of many types, such as family members, romantic love partners, close friends, and colleagues, which all belong to different categories. A second key component is that changes in neural representations are dependent on emotional responses toward the familiar individuals (Haxby & Gobbini, 2010). For example, Sugiura (2014) revealed different activation patterns in the perception of different familiar people. More extensive activations were observed in neural regions representing motivation, emotion, and rewards upon face perception of romantic love partners. Being exposed to an enemy's face recruited activations in the motor-associated cortices

and insula which reflect negative fearful responses and the preparation for attack or defense. Loss of a loved one activated the ventral striatum, a region shown to be responsive to the anticipation of aversive stimuli.

Since the neural activation of familiar faces is modulated by one's emotional response and knowledge to that person, patterns of neural activities varied depending on the emotional state and closeness to the personally-significant individual. Hence, it remains unclear whether a general neural network pattern exists for all familiar people.

Processing of Faces of Famous People

Previous studies revealed a double dissociation between face recognition and the processing of facial expression, as they are thought to function independently with very limited influence on each other (Calder, Young, Keane, & Dean, 2000). Nonetheless, recent literature demonstrated that processing of familiar face, specifically famous face, can be enhanced when typical emotions are presented. Kaufmann & Schweinberger (2004) investigated the effect of facial expression on famous face perception by using photos of celebrities; they reported that expression facilitates familiar face recognition as moderately happy expressions are recognized fastest. Kaufmann and Schweinberger (2004) found that since celebrities often exhibit moderately happy, rather than angry or sad, expressions, information for famous faces might be stored along with information about the 'typical' emotion. Thus, performance was better when the recognition of famous face is paired with typical expression, suggesting that famous face recognition preserve information about a typical emotional expression.

Neuroimaging Findings on Face Processing

Distinct Neural Processing for Novel and Familiar Faces

Lesion studies on prosopagnosia, a cognitive disorder where the ability to recognize familiar people from their faces is lost, indicated that the right hemisphere was associated with face recognition, as patients with right hemisphere lesions were unable to recognize familiar faces (Warrington & James, 1967). Subsequent studies attempted to localize the area of face recognition and dissociate the effect of familiar and novel faces among prosopagnosic patients. For example, Malone, Morris, Kay, & Levin (1982) encountered two prosopagnosic patients with different aspects of face recognition impairment. One patient improved recognition on familiar faces with no improvement in novel faces, whereas the other patient demonstrated improved performance in novel faces with no improvement in familiar faces. Such observation provided early evidence that the neural processing of familiar and novel face processing is, in fact, distinctive and dissociable.

Specific to Novel Face Processing

Since the neural processing of familiar and novel faces is shown to be different, recognition of familiar faces is believed to be much more complicated than novel face processing. It is based on the assumption that novel face processing involves only analysis of rudimentary facial features and representations, whereas familiar or personally significant faces often come alongside with biographical and emotional information as well. This, in turn, recruits extra brain resources from different brain regions and increases the complexity of familiar face processing. Functional neuroimaging studies revealed the occipital and temporal lobes, specifically the fusiform gyrus, inferior occipital gyrus, and superior temporal sulcus, respond more prominently in novel face perception (Natu & O'Toole, 2011). Besides the above regions, positron emission tomography (PET) study also revealed activations in the left amygdala in response to unknown faces perception

compare to known faces. Dubois et al. (1998) suggested the increased activations might be due to unknown faces being more aversive as these faces have no prior encounter.

Haxby and Gobbini (2010) found that stronger neural activations in the amygdala were evoked among faces of stranger relative to personally significant faces (e.g., friends and family members). They thought that the increased neural activities in the amygdala are associated with the increased alertness. Amygdala has generally been accepted as a region for memory formation with emotional events; it has been shown to be activated in aversive events. Hence, upon the perception of novel faces, the brain instantly prepares the individual to expect for possible aversive consequences, which brings about the amygdala activity.

Specific to Familiar Face Processing

Recent neuroimaging studies that have investigated familiar faces processing have found consistent neural activations in the fusiform gyrus, hippocampus, precuneus, prefrontal lobe, middle temporal gyrus using face identification tasks (Denkova, Botzung, & Manning, 2006; Neta & Whalen, 2011). fMRI study by Shah et al. (2001) found increased activations in the posterior cingulate cortex (PCC), including the retrosplenial cortex in response to the perception of familiar faces and voices. Recognition of familiar (famous) faces was associated with larger and widespread neural changes in the prefrontal, lateral temporal and medial temporal regions when compared with a newly learned face. (Leveroni et al., 2000). Involvement in the prefrontal lobe might be due to the fact that more neural resources are required for retrieving autobiographical information related to that particular face (Liu et al., 2013). Although familiar people can be divided into different categories, Sugiura (2014) pointed out that there is a large overlap between face and name recognition among common personally familiar people and romantic love partner. Early PET study by Sergent, Signoret, Bruce, & Rolls (1992) investigated activation differences

in the processing of known and unknown faces. They found activations in the anterior ventral-temporal region, including the right parahippocampal gyrus, when performing an identification task of famous faces. Recent neuroimaging studies revealed that personally familiar faces recruit limbic activations rather than the anterior temporal cortex (Henson et al., 2000), whereas recognition of famous faces specifically activates the temporofrontal cortex when compared with unknown faces (Sergent et al., 1992; Leveroni et al., 2000). Ramon, Vizioli, Liu-Shuang, & Rossion (2015) investigated the differences in neural responses to personally familiar and novel faces. Compared with novel faces, familiar faces elicit increased activation in the medial and anterior temporal regions, including the bilateral amygdala, right perirhinal cortex, right hippocampus and anterior inferior-temporal regions. Contrary to the view that initial determination of known-versus-unknown face occurs in the posterior face processing core regions, they believe that discrimination between personally familiar and novel faces emerge in the anterior ventral and medial temporal regions after initial analysis in the posterior core regions. Although there has been much research attempted to dissociate the underlying neural mechanisms of familiar and novel face recognition, discrepancies remain regarding the localization of neural regions for face recognition due to varying study paradigms and parameters.

Regarding famous face recognition, neural activations specific to famous faces generate are different relative to familiar faces. A recent study by Liu et al. (2013) found activations in the frontal and parietal regions, including the bilateral prefrontal cortex and right superior parietal lobe. They suggested that the enhanced activities observed in prefrontal cortex and superior parietal lobe are associated with storage and recollection of identity and autobiographical information, respectively, for famous faces. However, there is yet to be consensus on the neural activation

pattern of famous face recognition among the literature. Only one study has reported a lack of frontal lobe contribution when passively viewing famous faces (Ishai et al., 2002).

Summary of Neuroimaging Findings on Face Processing

Early lesion studies and patient studies on prosopagnosia revealed that the processing of familiar and novel faces is indeed distinctive and dissociable, which drove later researches into understanding the distinct neural mechanisms of novel and familiar face processing. Recent neuroimaging evidence demonstrated occipital and temporal activations, including fusiform gyrus, inferior occipital gyrus, and superior temporal sulcus, upon novel face processing. Familiar faces elicited an overall widespread and extensive activation compared with novel faces. Activation patterns differed slightly within the familiar face category. Specifically, activations were more prominent in the limbic system (e.g., PCC) for personally significant faces, whereas famous faces recruited the temporal and frontal activations.

Common Areas that Activate in Face Processing Regardless of Familiarity

Fusiform Gyrus

It has long been speculated that a specific region of the brain is responsible for the perception and processing of faces as neurophysiological studies in non-human primates (e.g., macaque monkeys) have revealed single neurons responsive to face stimuli in the inferior temporal cortex and superior temporal sulcus (Pourtois et al., 2004). Early PET study by Dubois et al. (1998) found fusiform gyri (FG) activation related to face perception, regardless of the type of tasks or the familiarity of faces. Activation in this area suggests that the FG is a possible region for the structural encoding phase in the Bruce and Young's model as this is the first essential step in face processing. They also found a right hemispheric specialization for face processing. Their result was consistent with the previous study which showed that the right FG responded more

substantially to famous faces than newly learned faces (Leveroni et al., 2000). Denkova et al. (2006) further verified functional lateralization of FG using fMRI: the left FG is more semantically-related, such as retrieving personal identity, whereas the right FG is associated with the processing of facial stimuli. Evidence from split visual field and prosopagnosia experiments also provided evidence for a right hemisphere lateralization for faces relative to objects (Eger, Schweinberger, Dolan, & Henson, 2005). When matching familiar and unfamiliar faces, the right FG is significantly activated, and the faces are more accurately matched, suggesting a behavioral advantage for familiar face perception in the right FG (Weibert & Andrews, 2015).

In another study, Liu et al. (2013) have shown enhanced FG activation to famous faces compared with common objects in prosopagnosic patients, suggesting the involvement of FG in the covert processing of familiar face. They suggested that FG alone is not sufficient for overt face recognition. Although famous faces showed more neural activation, the patient did not recognize the faces that he knew, suggesting that the neural activation in FG alone cannot lead to successful face identification (Liu et al., 2013).

In addition, other studies also found activations in the fusiform cortex upon the perception of emotional faces compared with neutral faces (Winston, Vuilleumier, & Dolan, 2003; Surguladze et al., 2003). Furthermore, Winston et al. (2004) have shown that fusiform cortex also encodes emotional states of the face, seeing an expressive face is thus activate FG.

Anterior and Medial Temporal Lobe

Early lesion studies demonstrated that damages in the anterior temporal lobe are frequently associated with semantic memory impairment for famous faces, voices, animals, buildings (Ellis, Young, & Critchley, 1989). Another study examining patients with Alzheimer's disease and medial temporal lobe amnesia revealed the high dependency between medial temporal lobe and

personally significant information (Westmacott, Black, Freedman, & Moscovitch, 2004). Denkova et al. (2006) provided neuroimaging evidence that medial temporal lobe is associated with the retrieval of autobiographical information, but not with the retrieval of semantic knowledge.

fMRI

To understand the neural activation and brain-behavior relationship associated with the processing of personally significant information in working memory, fMRI is used in this study. fMRI measures brain activity by detecting changes in blood flow in a non-invasive manner. Under the assumption that blood flow is coupled with neural activations due to metabolic activities, an influx of blood flow will be observed when a specific brain area is activated. In the context of fMRI, changes in blood flow are determined by the level of oxygenated blood, specifically hemoglobin level, and contrast with surrounding brain regions. These temporal changes in blood flow are captured by fMRI as signals referred to as blood-oxygen-level-dependent (BOLD) signals.

Captured BOLD signals are represented as voxels. Voxel is the basic unit of graphic information that defines a point a three-dimensional space, similar to pixels that define a point in a two-dimensional space such as images and photos. Since voxel is the representation of a basic unit in a three-dimensional space, it has x, y and z coordinate. Voxels are frequently used in the visualization and analysis of neuroimaging data to compare and contrast any significant activation in a specific area. Significant activation is determined by the number of nearby voxels, or cluster size, that demonstrate similar patterns. Different studies have different standards on the cluster size. For example, Leung & Alain (2011) have used a threshold cluster size of 196 μl or greater to be considered as significant activation.

Paradigm Design - Yoked design

As mentioned above, differences in neural activations emerge in familiar and novel face perception, it is essential to select faces that are specifically personally familiar to one individual yet unfamiliar to another individual for this study. Roye et al. (2010) used a yoked design to investigate neural processing of personally significant sound in human. In the yoked design, participants' ringtones were collected and used as stimuli, and ringtones of one participant was paired with ringtones of another participant. In this way, ringtones of one participant were served as personally significant sounds of that participant and novel sounds for another participant. Overall, this design allows an equal number of personally significant and insignificant information (e.g., sounds, pictures, photos, etc.) to be averaged across participants. In the current study, the yoked designed originated from Roye et al. (2010) was used by pairing familiar (personally significant) faces of one participant with another participant, thus creating a familiar (personally significant) and novel face condition, respectively. Details regarding photo selection, photo pairing, and yoked design will be further illustrated in the next chapter.

Rationales and Implications of the study

There were two motivations in this study. The first, and most important, motivation is to address the knowledge gap in the understanding of human working memory processing. As far as we know, working memory processing is broadly supported by the frontoparietal neural network. Specific neural circuits may be involved depending on the nature of stimuli, e.g., visual stimuli would lead to neural activity from the occipital or precuneus or auditory stimuli would be supported also through the temporal gyrus. However, almost all of the previous studies on working memory processing were conducted with the use of abstract stimuli like figures, patterns, tones, numbers, or letters, and rarely did they use stimuli that were meaningful or had significant personal

attachment to the individual. Indeed, processing of personally significant information is embedded in our everyday life. Hence, using an ecologically more valid stimulus, personally significant information, would help us understand the neural mechanism of working memory more comprehensively. The second motivation is to understand the brain-behavior relationship specific to the processing of personally significant information (faces) in working memory. Examining the brain-behavior relationship would allow us to distinguish the contribution of specific neural regions with respect to different patterns of behavioral performance during the processing of personally significant faces in working memory.

Investigation of working memory in the context of personally significant information has two potential implications. First, it provides unique scientific evidence guiding the use of a patient-centered approach for treatment and rehabilitation. Familiar stimuli (e.g., personally significant faces) are meaningful to each individual patient; our findings may provide an insight onto how that information could be used in designing tailor-made remedial activities or training programs for patients. Second, it helps explore the possibility of using familiar faces in cognitive training to enhance training outcome. Familiar faces might be better than artificial stimuli in facilitating or strengthening other cognitive functions when applied in working memory paradigms.

Objectives

There were two main objectives in this study. The first objective is to examine the neural activation of working memory under two different conditions: processing of personally significant faces versus processing of novel faces. The second objective is to examine the brain-behavior relationship in regions that are crucial for distinguishing the processing of personally significant faces in working memory. The results may provide insight onto the use of stimuli for inducing neural activity associated with working memory processing.

Chapter 2 Research Methodology

Participants

A convenience sample of 16 healthy Caucasian adults who met the eligibility of the study was recruited. Participants were recruited through means of poster advertisements (Appendix F), word-of-mouth around the University of Alberta campus in Edmonton, Canada. Interested individuals followed up by the research student and a research assistant upon satisfying the inclusion and exclusion criteria, which were listed as follow:

Inclusion Criteria

- No history of neurological (e.g., Alzheimer's disease, Parkinson's disease, multiple sclerosis) or psychiatric (e.g., Schizophrenia, bipolar disorder) disorders, cognitive or visual impairments;
- Right-handed and have normal or correct-to-normal vision;
- Currently not on any medication;
- Caucasians with English as their first language

Exclusion Criteria

- Magnetic Resonance Imaging (MRI) ineligible – presence of implanted cardiac pacemaker or any metal implants, pieces of shrapnel, aneurysm clips, or head wires or not satisfying with the safety criteria set by the MRI facility;
- Pregnant at the time of the experiment

All participants were interviewed and screened by members of the research team as well as MRI technicians from Peter S. Allen MR Research Centre to ensure safe exposure to fMRI using a screening questionnaire (Appendix E, Form E1/ E2). In addition, intake form (Appendix D) was completed, and written consent (Appendix C, Form C2) was obtained for each eligible

participant prior to the start of the study. Participants were informed about the right to withdraw from the study for any reason as well as data storage and confidentiality issues. Upon completion, all participants received a gift card to honor their time and effort dedicated to the study.

The rationale behind recruiting specifically Caucasian race is to reduce possible confounding bias due to differences in ethnicity. The term Caucasian might be too generalized and inclusive, however, it still makes up the majority of the Canadian population. To better represent the Canadian population and maximize the transfer of research knowledge, ethnicity of the majority Canadian population, which is the Caucasian ethnicity, was specifically selected for this study.

Sample Size

Initially, 16 participants were recruited to the study. The sample size was referred to previous studies of similar nature. However, there were two participants with excessive head movement or artifacts during fMRI scanning, and there was one participant with incomplete or missing data. Three more participants were later recruited to achieve the calculated sample size.

Face Working Memory Task – n-back Task

The face working memory task was designed based on the concept of n-back paradigm, where n=1 or n=2, and is a typical executive function task especially for assessing working memory (Leung & Alain, 2011). The image (visual stimulus) consisted of photos of human faces. Each image appeared on the screen in quick succession (Figure 2.2), with each image appearing for only 1 second before getting replaced by the next image (Figure 2.1). There were altogether four conditions, novel and familiar faces in 1-back and 2-back processing tasks.

In the 1-back task, participants were instructed to compare current face with the previous face (1 back) and press a button using the right index finger if both faces were the same; if the

faces were different then participants did not have to respond and continue the experiment by comparing the current face with the one before. In the 2-back task, participants were instructed to compare the current face with two faces before (2-back) and press the button if both faces were the same; if the faces were different, the participants did not have to respond and continue the experiment by comparing the current face with two faces before. Only novel or familiar faces were presented in a task, and the participants were not told of the familiarity until they see the images as the paradigm proceeds. There were six different runs of the n-back tasks, with three blocks of 1-back and 2-back condition each run arranged in a pseudo-randomized fashion (Figure 2.4). Each block consisted of 20 stimuli, with an average of 6 (ranging from 4 to 7 per block) targets or correct answers within each block. The total duration of each run was 8 minutes and 20 seconds, interleaved with 8 rest periods (six 26-second rest periods between blocks, one 44-second initial rest period and one 20-second rest period in the end) which served as a baseline measurement. The order of runs was determined in a pseudo-randomized fashion within the task (Figure 2.4). The sequence was determined using the random number generator in Excel. Besides the 6 blocks of the 1-back and 2-back condition, a block with scrambled faces was introduced at the end of each run to serve as a baseline measurement for fundamental visual perception. Scrambled faces referred to faces in which all facial features were moved from their original positions.

Details regarding the flow of each block were as follows: each block began with 2 seconds of instruction: participants were visually instructed whether they were doing 1-back or 2-back for the subsequent block. Each trial began with an image that lasted for 1 second, following a 1-second fixation cross. Participants were instructed to respond as fast as possible, button pressing during the image or the fixation cross were captured as a response. After 20 trials of stimuli, a rest period of 26 seconds appeared before the start of the next block with new instruction. Each block followed

the same flow till the end of the run, where the rest period was shortened in response to the tight 1-hour fMRI schedule.

Each face working memory task lasted 8 minutes and 20 seconds.

Photo Pairing and Preparation

Photo selection was based on the yoked design described by Roye et al. (2010). Each participant was to provide 12 photos of their close family members and friends, with 50% male and female to achieve gender balance. The following criteria were used to select eligible photos: 1) Faces must be clear and easily identified, 2) Faces not expressing extreme emotions, 3) Faces must be directly facing the camera. One set of photos with personally familiar faces (n=12) submitted by each participant was paired with a different set of photos (n=12) from another participant (Figure 2.3). This way, each face serves as a familiar face and as an unfamiliar face to the participants. Participants were grouped into different pairs through random assignment to minimize overlapping of personally familiar faces within the group.

The photos were first applied a gray scale filter with image size matched to ensure consistent face size and luminance across viewings (Shah et al., 2001). The backgrounds were cropped out, only face and hair was shown to each participant (Eger et al., 2005). The above photo preparation process was performed by the same research assistant using Adobe Photoshop CS one week prior to the scanning session. These photos were then used as familiar or novel face stimuli in the subsequent working memory paradigm during fMRI.

MRI Acquisition

Pre-fMRI Preparation

The one-hour fMRI session took place at the Peter S. Allen MR Research Center, which is located in the basement of the University of Alberta Hospital (Walter MacKenzie Centre, area

0A6). Participants were asked to remove any metal accessories and change to medical attire (e.g., Scrubs) provided by the MR facility. MRI technician then made a final safety screening before undergoing the fMRI session. The total time for the entire session lasted 1.5 hours and that included the 1-hour fMRI session, with an extra half an hour of acquiring participant consent, task training/ preparation, travel time, and fMRI equipment setup.

Different research personnel was responsible for the recruitment of participants and the conduction of assessment in order to minimize measurement bias based on participants' characteristics and groupings. Recruitment of participants was conducted by a research assistant, and the administration of the fMRI session was conducted by the student and the research assistant.

fMRI Preparation

After participants had cleared MRI safety from technicians, they were brought to the scanning room in preparation of the fMRI session. Participants were instructed briefly about the flow of the experiment, devices used for different tasks, as well as in the case of emergency before lying flat on the MRI bed. Participants were provided with attenuating headphones to minimize machine noise; a standard 8-channel bird-cage head coil was used for the detection of neural activations and extra foam padding on the sides to reduce discomfort and unnecessary head movement. These procedures were performed by the MRI technician.

Before the start of the experiment, Benson verified the devices used for the tasks were working properly (e.g., capturing signals without delay), set up the screen for the projector, and made sure proper display of the stimuli to the participants.

fMRI Scanning

A 1.5T Siemens Sonata MRI system with an 8-channel bird-cage head coil was used. Structural T1-weighted anatomical volumes were obtained before fMRI using SPGR (axial

orientation, TR = 2080 ms, TE = 4.38 ms, FOV = 256 mm, slice thickness = 1 mm). The duration for the T1-weighted imaging lasted approximately 6 minutes. During the T1-weighted imaging session, brain structures were examined in real time with the assistance of an MRI technician to identify possible structural abnormalities for future clinical notations and assessments.

After capturing structural images, participants performed six runs of the face working memory task within the one-hour fMRI session, in which functional T2-weighted imaging was performed using EPI acquisition (TR = 1950 ms, TE = 40 ms, flip angle = 90°, FOV = 256 mm, effective acquisition matrix = 64 × 64). Each functional sequence consisted of 36 4-mm thick axial slices, positioned to image the whole brain with a duration of 8 minutes and 20 seconds.

All tasks were run using E-Prime 2.0 Professional software (Psychology Software Tools, Pittsburgh, PA), with a Windows XP desktop computer in the MRI facility. The paradigms were displayed through a projector and screen, which was then perceived through the mirror installed in the bird-cage head coil.

Behavioral Data Analyses

Behavioral data including accuracy and reaction time were extracted from E-Prime 2.0 (Psychology Software Tools) for all runs within the n-back tasks. They were initially compiled using Microsoft Excel; behavioral analyses were performed using SPSS 24 for Mac (IBM Corporation, New York) for all individuals who completed the tasks. Accuracy refers to the percentage of trials that participants correctly responded out of all possible trials presented within the runs. Regarding the response time of each trial, only reaction times of the correctly responded trials were included in the calculation.

To examine the interaction between the familiarity (familiar vs. novel faces) and working memory load condition (1-back vs. 2-back), a general linear model using repeated measures was

set up in SPSS. The main effect of familiarity and working memory load was computed separately, and the interaction effect between the two factors was also assessed. If the main effect from a repeated measures analysis of variance (ANOVA) revealed statistical significance, follow up paired t-tests were conducted separately.

fMRI Data Analyses

fMRI Preprocessing

The functional images were preprocessed using the SPM8 software package (Wellcome Department of Cognitive Neurology, Institute of Neurology, Queen Square, London, UK), running under Matlab 7.14.0.739 (MathWorks, Natick, MA, USA). The first seven scans of each run were discarded manually to avoid any neural signal instability. The remaining scans (241 scans for n-back) of each run underwent five different image preprocessing steps to improve quality of images and standardize to a template for further analysis: 1) slice timing to correct image acquisition times between slices, 2) realigned with the first image to account for movement in the scanner, 3) co-registered the structural image to the mean functional images, 4) spatially normalized the functional and anatomical images to fit individuals' scan into MNI (Montreal Neurological Institute) template, and 5) smoothed to improve signal to noise ratio of the functional images and statistical power.

First Level Single Subject Analysis

The analysis was performed separately for each participant. First-level analysis refers to the fMRI analysis at the individual level; it was performed after image preprocessing steps. A mixed model design (block and event related) was used for n-back. Refined fMRI images were allocated into different runs within the model, and each condition (1, 2-back, rest, scramble) was defined according to different onset timing for each block. An advantage of the block design is a

better signal-to-noise ratio compared to a pure event-related design. However, activations from block design might not be as specific to the trials itself.

After the first level analysis, T contrast analysis for pairwise comparisons was set up to investigate the relationship between certain conditions and neural activations. T contrast can reveal significance for the n-back task, there were three contrasts set up for each participant: 2-back versus 1-back, 2-back versus rest, 1 versus rest. 2-back vs. 1-back intended to examine the effect of cognitive load (harder versus easier task) on working memory network; whereas 2-back vs. rest and 1-back vs. rest contrasts were to tease out the cognitive network for both 2-back and 1-back respectively as the rest condition serves as the baseline measurement. After setting up the T contrasts, each individual had three pairs of working memory contrasts for second-level group analysis.

Second Level Group Analysis

Second-level analysis refers to the between-subject fMRI analysis, which compiles and average individual contrasts to compare the effects between groups of individuals. It is often used to observe whether effects seen at the individual level are also likely to be found in a population. It began with averaging the beta value for all the contrasts produced at the first-level analysis. T contrast files regarding the effect of cognitive load (2-back vs. 1-back) and familiarity (familiar vs. novel) were averaged and yielded group results using a 2x2 factorial design.

ROI Analysis

Apart from the whole-brain analysis, we also conducted ROI analysis to pinpoint the underlying relationship between certain brain regions in response to specific cognitive conditions. The rationale behind this analysis is to 1) verify neural activation findings from whole-brain

analyses, 2) identify specific brain areas in response to a particular condition in the context of the n-back working memory task.

MarsBaR is an ROI toolbox for SPM, which is widely used to perform ROI analysis among the neuroimaging field such as fMRI. The present study conducted ROI analysis using MarsBaR version 0.44 implemented on Matlab version 7.14.0.739, and these were the steps followed to perform ROI analysis: 1) select the ROI of interested regions provided by Marsbar 2) select the corresponding contrast images to generate ROI values 3) extract ROI values into Excel spreadsheet 4) organize the values in a way to be able to copied into SPSS for statistical analysis.

A total of 21 brain regions were identified, activations from both hemispheres were included in the ROI analysis (Table 2.1). The following brain regions were identified from whole-brain analyses and were chosen to perform ROI analysis: frontal lobe (superior medial frontal gyrus, superior frontal gyrus, middle frontal gyrus, inferior frontal gyrus, medial frontal gyrus), parietal lobe (inferior parietal lobule, precuneus), temporal lobe (middle temporal gyrus, inferior temporal gyrus, parahippocampus, FG), occipital lobe (superior occipital gyrus, middle occipital gyrus, inferior occipital gyrus, culmen), subcortical (ACC, PCC, thalamus, insula), cerebellum (crus 1 and crus 2).

Chapter 3 Results

A convenience sample of 16 healthy Caucasian adults (7 males; mean age 20.4 ± 1.8 years; age range = 18 to 25 years; 14.1 ± 1.5 years of education) who met the eligibility of the study were recruited (Table 3.1).

Behavioral Performance

Table 3.2 summarized the overall behavioral performance on 1-back and 2-back conditions with familiar and novel face stimuli. Comparison between working memory load and familiarity was presented by bar graphs in Figure. 3.1 for hit accuracy/ reaction time, and Figure 3.2 for false alarm/ reaction time.

Hit Accuracy and Reaction Time

Repeated measures ANOVA performed on percent accuracy indicated a significant main effect of working memory load ($F(1, 15) = 17.173$, $p = .001$, $\eta^2 = .534$) and load x familiarity interaction effect ($F(1, 15) = 7.855$, $p = .013$, $\eta^2 = .344$). However, there was no main effect for familiarity ($F(1, 15) = 3.64$, $p = .076$, $\eta^2 = .195$). Follow up analysis using paired-samples t-tests revealed statistical significant differences between 2-back and 1-back conditions among familiar faces; $t(15) = 3.080$, $p = .008$. Similarly, accuracy of 2-back significantly differed from 1-back condition among novel faces; $t(15) = 3.813$, $p = .002$.

Repeated measures ANOVA for hit reaction time also revealed a significant main effect of working memory load ($F(1, 15) = 39.874$, $p = .000014$, $\eta^2 = 0.727$). Again, there was no main effect for familiarity ($F(1, 15) = .183$, $p = .675$, $\eta^2 = .012$). Moreover, there was no load x familiarity interaction effect ($F(1, 15) = .276$, $p = .607$, $\eta^2 = .018$). Paired-samples t-tests revealed statistical significant differences in 1-back compared with 2-back condition among familiar faces;

$t(15) = 4.489$, $p = .000433$. Statistical significant differences were also found among novel faces between 1-back and 2-back conditions; $t(15) = 7.089$, $p = .000004$.

False Alarm and Reaction Time

Repeated measures ANOVA for false alarm also revealed a significant main effect of working memory load ($F(1, 15) = 10.359$, $p = .006$, $\eta^2 = .408$). However, there was no main effect for familiarity ($F(1, 15) = 2.18$, $p = .16$, $\eta^2 = .127$) or load x familiarity interaction effect ($F(1, 15) = 7.929$, $p = .013$, $\eta^2 = .346$). Paired-samples t tests revealed statistical significant differences among novel faces between 2-back and 1-back conditions; $t(15) = 4.215$, $p = .001$.

Repeated measures ANOVA for false alarm reaction time revealed a significant main effect of working memory load ($F(1, 15) = 8.688$, $p = .01$, $\eta^2 = .367$) and familiarity ($F(1, 15) = 12.589$, $p = .003$, $\eta^2 = .456$). However, there was no load x familiarity interaction effect ($F(1, 15) = 1.407$, $p = .254$, $\eta^2 = .086$). Follow up paired-samples t tests revealed statistical significant differences among novel faces between 2-back and 1-back conditions; $t(15) = 2.863$, $p = .012$. Statistical significant differences were also demonstrated in the 2-back condition between novel and familiar faces; $t(15) = 2.992$, $p = .009$.

Summary of Behavioral Findings

To briefly summarize the above statistical analyses, our behavioral data demonstrated that, relative to novel faces, familiar faces were more accurately identified in the 2-back condition. On the contrary, novel faces were more prone to false alarms when compared with familiar faces. This suggested that familiarity plays an important role during working memory task that requires high cognitive demand.

Our data for reaction time showed faster responses in the 1-back condition compared with the 2-back condition, suggesting that cognitive load, rather than familiarity, plays a role in reaction

time. When comparing false alarm reaction time, however, novel faces triggered slower responses than familiar faces, suggesting that face familiarity plays a role in reaction time only upon mistakes.

fMRI Results

Main effect of working memory load (2-back vs. 1-back) and familiarity (novel vs. familiar) was set up to determine activation significance between working memory load and familiarity of face stimuli. Table 3.3, Figure 3.7, Figure 3.8, and Figure 3.9 illustrated the fMRI results for the main effect of working memory load, familiarity, as well as the load x familiarity interaction effect. Statistical threshold was set to be $p < .001$.

Main Effect of Working memory load. For the 2-back > 1-back comparison, fMRI changes were found on the typical working memory network, consisting bilateral frontal (BA 6/10/11) and inferior parietal lobe (BA 40) activations. Subcortical structures, including bilateral insula (BA 47), thalamus, cingulate cortex, as well as cerebellum (crus 1/8) were found to be activated. For the 1-back > 2-back comparison, clusters of activations in the temporal regions were found, specifically right middle temporal pole (BA 21) and right hippocampus (BA 20). Activations were also found in the left ACC (BA 11) and right insula (BA 48).

Main Effect of Familiarity. Right ACC was the only cognitive region that demonstrated fMRI signal differences in the familiar > novel comparison. There was no main effect of familiarity in the novel > familiar comparison.

Interaction Effect. Load x Familiarity interaction effect revealed fMRI signal changes in the frontal and temporal regions, consisting left superior frontal gyrus (BA 32), right inferior frontal gyrus (BA 47), right medial frontal gyrus (BA 10), as well as right inferior temporal gyrus (BA 20) and left parahippocampal gyrus (BA 20). Activations were also found in the bilateral thalamus and left cerebellum (Crus 2).

Pairwise T-contrast

Group analysis using one-sample t-test was performed on each of the four contrasts (familiar 1-back (F1), familiar 2-back (F2), novel 1-back (N1), novel 2-back (N2) generated in the first-level analysis, these contrasts were namely: N2 vs. N1, F2 vs. F1, N2 vs. F2, and N1 vs. F1. Refer to Table 3.4 and Table 3.5 for a detailed list of loci of activations, with a statistical threshold of $p < .001$. Figure 3.10, 3.11 and 3.12 demonstrate a visual representation of fMRI results.

Load-related Activation

Novel 2-back > Novel 1-back. This contrast aimed to reveal neural changes related to working memory load in the context of novel face stimuli. Novel faces demonstrated bilateral activations in the frontal and parietal regions, activating a typical working memory neural network. Regions activated include bilateral inferior frontal gyrus (BA 47/45), right superior frontal gyrus (BA 11), as well as left inferior parietal lobe (BA 39) and right superior parietal lobe (BA 7). Besides, extensive bilateral activations were also demonstrated in the thalamus.

Familiar 2-back > Familiar 1-back. This contrast aimed to reveal neural changes related to working memory load in the context of familiar face stimuli. Similar to the 2-back > 1-back contrast for novel faces, this contrast also revealed the typical frontoparietal working memory network, specific regions activated include bilateral superior frontal gyrus (BA 6), left middle frontal lobe (BA 45/11), also the left inferior parietal lobe (BA 7). Besides the typical frontoparietal activations, significant activations were also found in the left cerebellum (crus 1 and crus 2).

Familiarity-related Activation

Novel 2-back > Familiar 2-back. This contrast investigated neural changes associated with face familiarity in high working memory load condition. Prominent activations were found in the

frontal and parietal areas, specifically the left inferior frontal gyrus (BA 45) and superior parietal lobe (BA7). Clusters of activations were also found in the left insula region (BA 47).

Familiar 2-back > Novel 2-back. This contrast investigated neural changes associated with face familiarity in high working memory load condition. Significant neural activations were only found in the ACC (BA 11).

Novel 1-back > Familiar 1-back. This contrast was performed to show changes related to face familiarity in low working memory load condition. There was not any significant activation shown in this contrast.

Familiar 1-back > Novel 1-back. The contrast was examined with an aim to reveal neural changes related to familiarity in low working memory load condition. Extensive activations were found in the frontal regions, including the superior frontal gyrus (BA 32), middle frontal gyrus (BA 9) and medial frontal gyrus (BA 11). Besides the frontal lobe, the contrast also revealed substantial activations in the middle cingulate cortex (BA 23), insula (BA 48), thalamus, and cerebellum.

Attention-related Activation

Novel 1-back > Novel 2-back. This contrast was examined to show changes related to attention in the context of novel face stimuli. Prominent neural activations were seen in the bilateral superior temporal lobe (BA 38/ 48), middle and superior temporal pole (BA 20/38). Significant activations were also found in the left FG (BA 20), right hippocampus (BA 20), and left ACC (BA 11).

Familiar 1-back > Familiar 2-back. This contrast was examined to show changes related to attention in the context of familiar face stimuli. Activations were mainly clustered in the face perception areas, including middle and superior temporal lobe (BA 22), inferior and superior

occipital lobe (BA 17/ 18), and FG (BA 37). Moreover, extensive activations were found in the ACC (BA 32), inferior and superior frontal gyrus (BA 32/38/47), and parahippocampal regions (BA 20/30).

Scramble > rest. This contrast was examined to show changes related to basic visual processing (Table 3.6). Clusters of neural activations were substantially observed in the frontal, temporal, and occipital lobe, including the bilateral inferior frontal gyrus (BA 44/ 48), left superior temporal pole, and bilateral occipital gyrus (BA 18/ 19).

Summary of fMRI Findings

Overall fMRI results in load-related activations demonstrated a typical frontoparietal working memory network, including the superior, middle frontal gyrus, and the inferior parietal lobe for both familiar and novel faces. Familiar faces also activated the cerebellum, whereas novel faces activated the thalamus. For familiarity-related activations, activations in the frontal, parietal and temporal regions were found in low cognitive demand 1-back condition, only ACC activations were found in the 2-back condition.

ROI Results

A set of regions were identified for further ROI analysis, see Table 2.1 for a detailed list of regions selected for ROI analysis.

Correlation between Signal Activity for F2 > N2 and Accuracy and Reaction Time

Table 3.7 illustrated the results of the correlation. Regarding hit accuracy, strong positive correlation in hit accuracy was found in the left inferior frontal gyrus (r = .629, p = .009) and superior occipital gyrus (r =.712, p = .002). Strong negative correlation in reaction time was found in the left ACC (r =-.681, p = .004). Figure 3.3, as well as Table 3.7, revealed a clear dissociation between accuracy and reaction time among regions of interest in the F2 > N2 comparison: all

regions examined exhibited positive correlation with hit accuracy, and negative correlation with reaction time.

Correlation between Signal Activity for Conditions > rest and Accuracy

(Conditions: F1, F2, N1, N2)

Table 3.8 illustrated the results of the correlation. Strong positive correlation was found in the right inferior temporal gyrus (r = .659, p = .005) and left inferior occipital gyrus (r = .728, p = .001) in the F2 condition for hit accuracy. Besides F2, other conditions except for N2 also demonstrated significant positive correlation in the frontal and temporal regions (Table 3.8). The only negative correlation was found in the left superior medial frontal gyrus (r = -.516, p = .041) in N2 condition. Figure 3.4 demonstrated an opposing pattern in signal change between F1 and N2 hit accuracy: signal change was positively correlated in F1, negatively correlated in N2.

Correlation between Signal Activity for Conditions > rest and Reaction Time

(Conditions: F1, N2)

Table 3.9 illustrated the results of the correlation. Clusters of regions demonstrated strong negative correlation in the F1 condition for hit reaction time, including bilateral FG, right parahippocampus, bilateral superior occipital gyrus, left middle occipital gyrus, left inferior occipital gyrus, and bilateral culmen. Significant positive correlation was found in left frontal gyrus and cingulate cortex in N2 condition. Figure 3.4 and 4.7 demonstrated the negative correlation of reaction time in F1, positive correlation of reaction time in N2.

Chapter 4 Discussion

The aim of the study was to understand the neural mechanism of working memory using personally significant information. Behavioral data demonstrated that both familiarity and working memory load contributed to working memory performance. Familiar faces were more accurately identified than novel faces in high working memory load condition, faster reaction time was observed in low working memory load condition. fMRI results demonstrated a typical frontoparietal working memory network in both familiar and novel faces. In addition, familiar faces activated the cerebellum, whereas novel faces activated the thalamus. ROI results revealed a dissociable pattern of brain-behavior relationship: neural activations for F2 showed a positive correlation with hit rate and negative correlation with reaction time across the frontal, occipital and limbic regions, whereas N2 showed a negative correlation with hit rate and positive correlation with reaction time in frontal regions.

Typical Frontoparietal Network in Processing of Novel Faces in Working Memory

It is no surprise that 2-back is cognitively more demanding than 1-back condition, as many previous studies found activations robustly in the frontal and parietal areas with respect to task demand. Our behavioral results also demonstrated a main effect of working memory load (*2-back > 1-back*) on both familiar and novel faces. fMRI results from the *Novel 2-back > Novel 1-back* contrast (Table 3.4; Figure 3.11) revealed a typical frontoparietal working memory network, specific regions included the dorsolateral prefrontal cortex (BA 8), ventrolateral prefrontal cortex (BA 45, 47), premotor cortex (BA 6), superior and inferior parietal lobe, as well as thalamus (Table 3.4). Brain regions from our data are consistent with recent neuroimaging literature on working memory (Owen et al., 2005; Wager & Smith, 2003). A meta-analysis by Owen and colleagues (2005) compiled previous working memory studies that used n-back as their experimental

paradigm and reported cortical regions that were commonly activated, including the premotor cortex, dorsolateral and ventrolateral prefrontal cortex, as well as parietal cortex and thalamus.

Owen et al. (2005) also found out that n-back tasks using nonverbal stimuli (e.g., faces) showed a lack of activations in the left ventrolateral prefrontal cortex. Our fMRI results showed activations in the ventrolateral prefrontal cortex and bilateral inferior frontal gyrus (BA 45/47). However, *Novel 2-back > 1-back* contrast from Table 3.4 revealed that activations were more extensive in the right hemisphere (357 voxels) relative to left hemisphere (195 voxels). Although not entirely a lack of left prefrontal cortex activations, our results showed a right-lateralized neural pattern during working memory task with novel faces, which is congruent with the results from the working memory meta-analysis by Owen et al. (2005).

Cerebellar Involvement in Processing of Personally Significant Faces in Working Memory

The fMRI results also indicated a frontoparietal working memory network when processing personally significant faces during n-back task. Moreover, cerebellar activations were also observed, specifically in the cerebellum VI, Crus 1 and Crus 2 regions. Traditional view on the function of the cerebellum as modulating motor behaviors has been well characterized over the past decades (Paulin, 1993; Manto et al., 2012). However, recent anatomical and neuroimaging studies began to reveal other cognitive functions of the cerebellum. Recent evidence showed that the role of cerebellum might not be limited to motor behavior regulation, but also in language (de Smet, Paquier, Verhoeven, & Mariën, 2013), working memory (Hayter et al., 2007), and social cognition (Van Overwalle, Baetens, Mariën, & Vandekerckhove, 2014). A functional neuroimaging study by Caulfield, Zhu, McAuley, & Servatius (2016) investigated the cerebellar response to familiar and novel stimuli. They found that familiar stimuli (faces and scenes) activated more robustly in cerebellum I-IV, V, VI, as well as Crus 1 and Crus 2 relative to novel stimuli.

Our results yielded congruent results in which cerebellum VI, Crus 1, and Crus 2 were activated in the *Familiar 2-back > Familiar 1-back* contrast (Table 3.4; Figure 3.10). This confirms previous findings that familiar stimuli (faces/ scenes) elicit cerebellar responses, especially in cerebellum VI, Crus 1, and Crus 2. Our results further demonstrated that personally significant faces, which is a kind of familiar stimuli, also activated the same cerebellar sub-regions.

Anterior and Posterior Cingulate Cortex in response to Personal Familiarity and Working Memory

Behavioral data showed significant differences between familiar and novel faces in high working memory load (2-back), performance was much more accurate on personally familiar faces relative to novel faces (Figure 3.1A). fMRI data also demonstrated a main effect of familiarity (*Familiar > Novel*), only the right ACC was activated (Table 3.3; Figure 3.8). Previous studies showed multifaceted aspects of cognitive functions in ACC. One study (Gray & Braver, 2002) pointed out that increased ACC activations upon high working memory load, indicating that neural activations of ACC are modulated by working memory load. A recent study revealed a linkage between personally familiar information and neural activities in ACC. Bobes, Lage Castellanos, Quiñones, García, & Valdes-Sosa (2013) demonstrated large and prolonged neural responses in the extended face processing system exclusively to personally significant faces, which included ACC, PCC, and medial orbitofrontal cortex. These areas, however, responded very weakly upon unfamiliar and newly-learned faces. They suggested that ACC activations might be associated with emotional experiences with personally significant individuals, as previous studies (Waugh et al., 2010; Cato et al., 2004) also showed increased hemodynamic responses in ACC and PCC when affective pictures or words were presented. This study confirms previous findings that ACC activations were related to the emotional experiences upon perceiving personally significant

information, it is also reasonable to evoke emotional responses automatically to individuals who are closely associated with the participants. Lack of ACC activations in novel faces in this study further confirmed ACC's association with personally familiar information. Pairwise T comparison revealed ACC activations from the *Familiar 2-back > Novel 2-back* contrast, illustrating that the effect of familiarity was only observed in high working memory load condition. Our results replicated two aspects of ACC functions previously found: working memory and personal familiarity. Neural activity of ACC was associated with both increased working memory load and personally familiar information.

Besides ACC, PCC is often associated with personally familiar face perception as it is considered part of the extended system for face perception and processing. Previous work found PCC activations among personally significant faces. One study (Shah et al., 2001) demonstrated increased amodal PCC activations by passively viewing faces or hearing voices of personally familiar individuals, suggesting that PCC might be related to familiarity checking and identity recognition. Our study did not yield PCC activations upon perceiving of personally familiar faces.

More Effort in Processing Novel Faces in High Working Memory Load

Some studies suggested that familiar faces are more complex relative to novel face processing, while some suggested that novel face processing is more complicated due to the deployment of attention and effort to construct new facial representations (Natu & O'Toole, 2011). Our behavioral data showed significant differences in mean accuracy between familiar and novel faces in 2-back condition (Figure 3.1A), that is, familiar faces are processed more accurately that novel faces in high working memory load. Our fMRI results also revealed that relative to personally significant faces, working memory involving novel faces elicited a more extensive and widespread frontoparietal working memory network, including the dorsolateral prefrontal cortex

(middle frontal gyrus), ventrolateral prefrontal cortex (inferior frontal gyrus), as well as inferior parietal lobe and thalamus. In the *2-back > 1-back* contrast, novel faces in general recruited larger and more widespread neural activations in the frontal and parietal regions. *Novel 2-back > Familiar 2-back* high working memory load contrast also demonstrated stronger frontal and parietal activations in novel faces. Taken together, it seems that both face conditions elicit the typical frontoparietal working memory network, but novel faces seem to recruit more widespread working memory activations. It is likely that novel face processing is more challenging and required more effort, as shown from the dampened accuracy relative to familiar faces, as well as increased neural activations in the overall frontoparietal working memory network.

ROI Findings between Personally Significant Faces and Novel Faces

Our fMRI results revealed a main effect of familiarity in the right ACC (Table 3.3; Figure 3.8); further pairwise T comparison also confirmed the involvement of ACC in the processing of personally significant faces relative to novel face processing in 2-back condition (Table 3.4). ROI analysis showed that hit accuracy and reaction time are correlated with signal change in various brain regions (Table 3.7). Our ROI results demonstrated a dissociation of activation behavior between familiar and novel faces. Table 3.7 revealed a positive correlation with hit accuracy in frontal, temporal, occipital gyrus as well as FG; negative correlation with reaction time in prefrontal, occipital gyrus, ACC, and hippocampus. Regarding reaction time, ROI table for *Familiar 2-back > Novel 2-back* (Table 3.7) and *Novel 2-back > rest* (Table 3.9) revealed commonly activated regions including the left superior medial frontal gyrus and left ACC. In Table 3.7, neural activations were negatively correlated with task performance in familiar faces, which means a decrease in neural activations in response to faster reaction time. On the contrary, the same regions were positively correlated with task performance in novel faces, meaning that an

increase in activations in response to slower reaction time. It seems that personally significant information in working memory have a facilitating effect on neural activities since activations are associated with better accuracy (positive correlation) and faster reaction time (negative correlation). Past behavioral study has demonstrated enhanced visual working memory performance and capacity in familiar (famous) face perception relative to unfamiliar face perception (Jackson & Raymond, 2008), suggesting that visual working memory can be enhanced if prior visual representations exist in long-term memory. Our behavioral results also revealed congruent findings, that is, better performance in familiar faces relative to novel faces under the 2-back high working memory load condition. Therefore, it is likely that extensive neural activations in prefrontal, temporal, occipital gyri are a result of enhanced behavioral working memory performance.

More Widespread Neural Activations in Familiar Faces in Low Working Memory Load

A previous study by Leveroni et al. (2000) demonstrated larger and widespread neural changes in the prefrontal, lateral temporal and medial temporal regions when compared familiar (famous) faces to newly learned faces or unfamiliar faces. Our study yielded congruent results. From the *Familiar 1-back > Novel 1-back* low working memory load contrast, extensive neural activations were found in the prefrontal cortex (BA 32, 11, 9), as well as medial temporal cortex (BA 48). However, the reverse contrast *Novel 1-back > Familiar 1-back* did not demonstrate any significant neural changes. This confirms that familiar faces elicit a larger neural response relative to novel or newly-learned faces. Some studies pointed out familiar face processing requires more complicated cognitive processing due to additional emotional and episodic memories attached, whereas others believe novel face processing requires extra cognitive resources due to the extra attention required and a lack of prior face representation (Natu & O'Toole, 2011). In contrast, our

behavioral results revealed no main effect of familiarity between personally familiar and novel face processing in 1-back condition (Figure 3.1A), mean accuracy between the two were also comparable in 1-back condition (Table 3.2). Under the assumption that more effortful cognitive processing can be reflected from dampened task performance and extensive neural activations, it seems that familiar face processing cannot be concluded to be more effortful relative to novel face processing. It seems that a larger neural response from familiar face processing might be related to the fundamental differences in emotional and episodic experiences that lie between the two. Taken together, it seems that the prefrontal and medial temporal cortex are essential cognitive regions for familiar face perception, regardless of famous or personally familiar individuals.

Lack of Fusiform Face Area in Face Perception Contrast

Ample neuroimaging evidence from the recent literature on face processing have demonstrated the face-preferential aspect of the fusiform face area (FFA), by exhibiting large and prolonged neural responses to faces in various face recognition tasks. Regarding the effect of familiarity on the FFA, however, previous work yielded ambivalent results. Some reported increased FFA activations in personally familiar faces (Shah et al., 2001), others reported a reduced FFA activation in famous faces (Leveroni et al., 2000). Our study did not have activations in the FFA. One reason for the lack of activations in the FFA might be due to the subtraction method that we used for fMRI. According to the subtraction method, neural activations are based on relative magnitudes of neural responses from one condition to another. Since FFA are shown to be specifically tuned to faces, regardless of familiarity, it is likely that FFA activations are seen in both personally significant faces and novel faces. FFA activations in both conditions would then be 'eliminated' after pairwise T comparison due to similar activation magnitude.

Lack of Medial Temporal Activations among Novel Face Working Memory

Previous studies (Hasselmo & Stern, 2006; Stern et al., 2001) on working memory with novel information demonstrated extended activations in the medial temporal region in addition to the typical frontoparietal network when processing novel information while performing working memory paradigm. Familiar information, as they suggested, is not as cognitively demanding as novel information and merely the frontoparietal working memory network would suffice. Novel information, however, requires extra cognitive resources from the medial temporal region, specifically entorhinal and parahippocampal regions, in order to maintain high cognitive demand. Our results did not suggest temporal activations in novel face perception. One reason might be due to the definition of novelty, as these studies defined novelty as abstract items with no prior exposure, they believed that letters, digits or even faces of strangers are considered familiar due to prior exposure of the same construct. According to this belief, both personally significant faces and unfamiliar faces would be considered as familiar. Moreover, these studies utilized objects and scenes, rather than faces, as their stimulus. Evidence has shown that neural activations are stimulus-specific, that means a specific type of stimulus in specific modality recruits neural activities from specific cognitive regions. It has been shown that objects recruit the occipital face area, whereas faces recruit FFA. Differences in the definition of novelty, as well as different stimulus modality, might explain a lack of medial temporal activations upon novel face perception in our study.

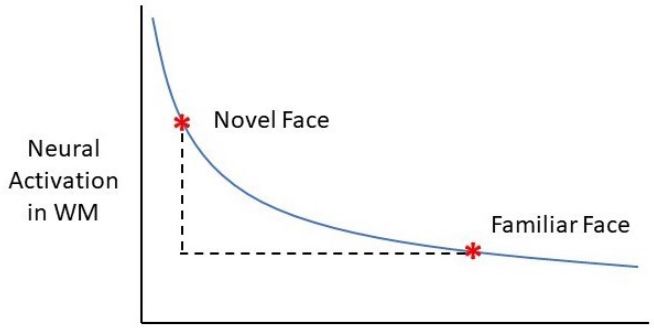
Lack of Hippocampal/parahippocampal Activations among Novel Face Working Memory

Using novel faces, one study found hippocampal and parahippocampal activations in a delayed-recognition working memory task during delayed and retrieval stage, respectively (Ranganath & D'Esposito, 2001). This is inconsistent with our data results. One explanation could

be that differences in working memory paradigm. It is rather challenging to break down working memory into different sub-stages in the n-back task since stimuli occur in quick succession. Besides, the fMRI contrast is against a long fixation baseline, whereas in our study it is always another pair of face/ load conditions.

Implication of the Study – Cognitive Training

Our study provided scientific evidence to illustrate the underlying differences in neural mechanisms between personally significant faces and novel faces while performing working memory tasks: novel faces recruited more extensive and widespread frontoparietal working memory network relative to personally significant faces. However, familiar faces activated more robustly in low working memory load/ fundamental face processing, which is a congruent finding with the previous face processing studies. For treatment and rehabilitation, it is possible to engage in a patient-centered approach to cognitive training, such as working memory training using personally significant faces in an n-back task. In order to induce neuroplasticity in different cognitive areas, it is reasonable to use novel faces due to the widespread neural activations during working memory tasks. However, to induce neuroplasticity for fundamental face processing, it might be better to use familiar faces in order to activate more brain regions. Future study on a training paradigm is needed to confirm this suggestion.



Limitations

Some limitations of this study are worth mentioning. Firstly, a lack of a consistent match in the demographic background among participants and small sample size are limiting factors for this study; future studies should aim at a larger sample size to minimize possible bias. Secondly, age range and gender balance of the personally significant faces were not restricted. This was not controlled due to a limited selection of photographs for 12 familiar faces. Faces of family members and close friends might be another limitation because these faces usually trigger positive emotional responses. It might be worthwhile to investigate the neural activity on the other side of the spectrum, by perceiving faces of personally significant individuals yet trigger negative emotions (e.g. personally well-known enemies). For example, previous studies (Sugiura, 2014) demonstrated that perceiving romantic love partner's faces elicit neural activations in the motivation, emotion, and reward centers of the brain while perceiving an enemy's face activates the motor-associated regions in preparation for motor responses (e.g. attack or defense).

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APPENDIX A FIGURES

Figure 2.1. Boxcar diagram for the n-back paradigm. An overview of the n-back paradigm in one run. Each run consisted of 6 blocks of 1-back or 2-back in either familiar or novel faces, with one block of scrambled faces at the end. Each block contained 20 trials, lasting 40 seconds. Each rest period lasted 26 seconds, except for initial and final rest which lasted 44 seconds and 20 seconds, respectively. Total duration of one complete run lasted 8 minutes and 20 seconds.

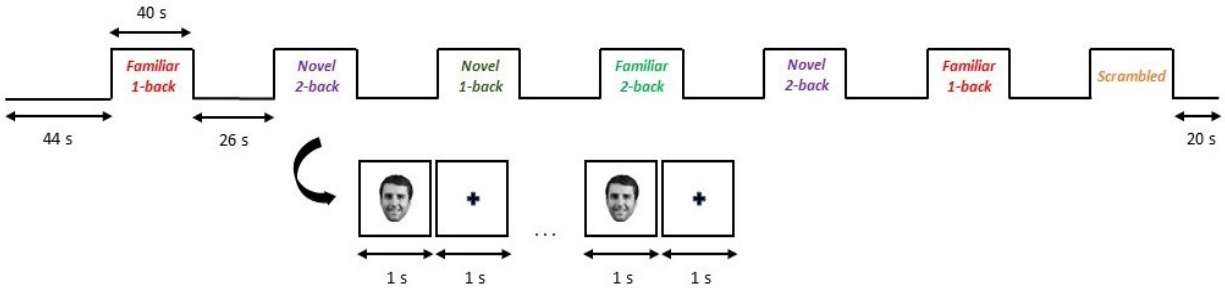


Figure 2.2. Flow of the n-back paradigm. n-back were used for investigating working memory function. Greyscale photos of different faces were presented to each participant sequentially. Participants were required to compare the current stimulus with the previous (1-back) or two stimuli before (2-back).

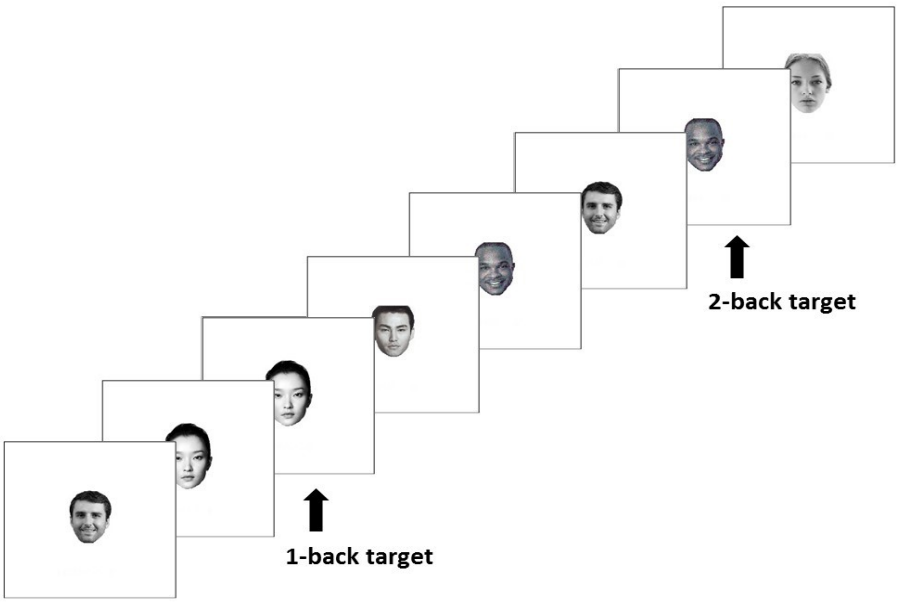


Figure 2.3. Photo pairing of personally familiar and novel faces. Each participant was required to submit photos (n=12) of personally significant individuals. A set of photos from Person A was paired with Person B, faces familiar to Person A would be unfamiliar to Person B, and vice versa.

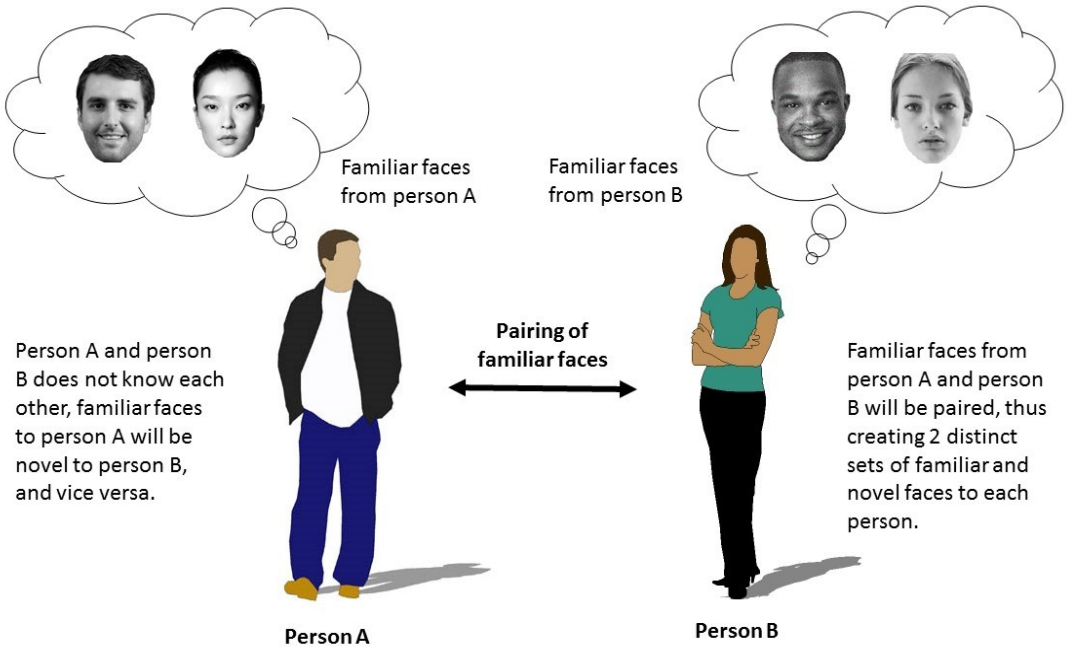
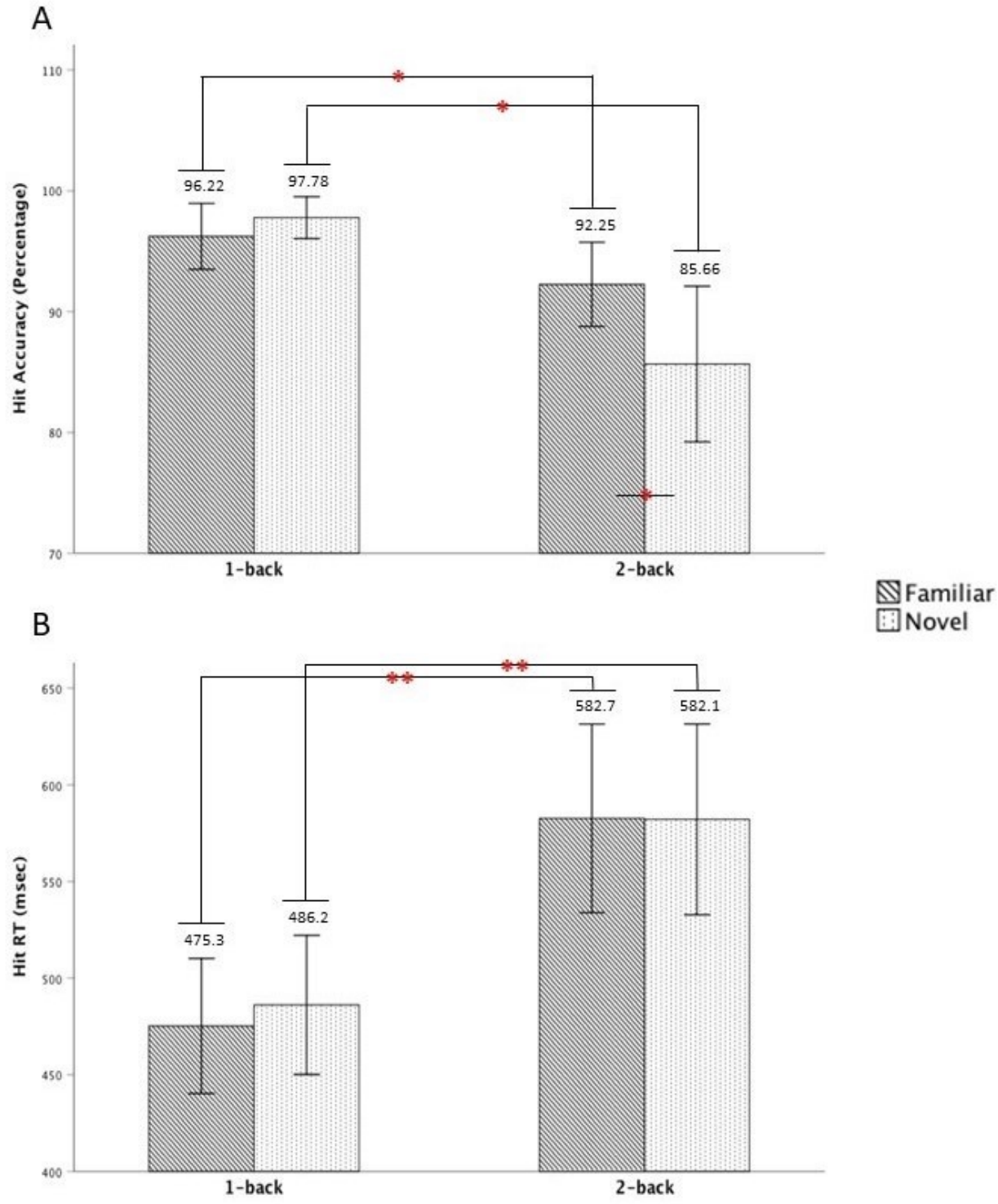


Figure 2.4. Block order for different runs of n-back task. The four conditions (F1, F2, N1, N2) equally split a total of 36 blocks within the 6 runs of n-back, with each condition consisted of 9 blocks across all 6 n-back runs.

Block / Run	1	2	3	4	5	6
1	F2	N1	F2	N1	F1	N2
2	F1	F2	N1	N2	N2	N1
3	N2	F1	N2	N1	F2	N1
4	N1	F1	N2	F1	F2	F2
5	N2	F2	F1	N2	N1	F1
6	F1	N2	F1	F2	N1	F2

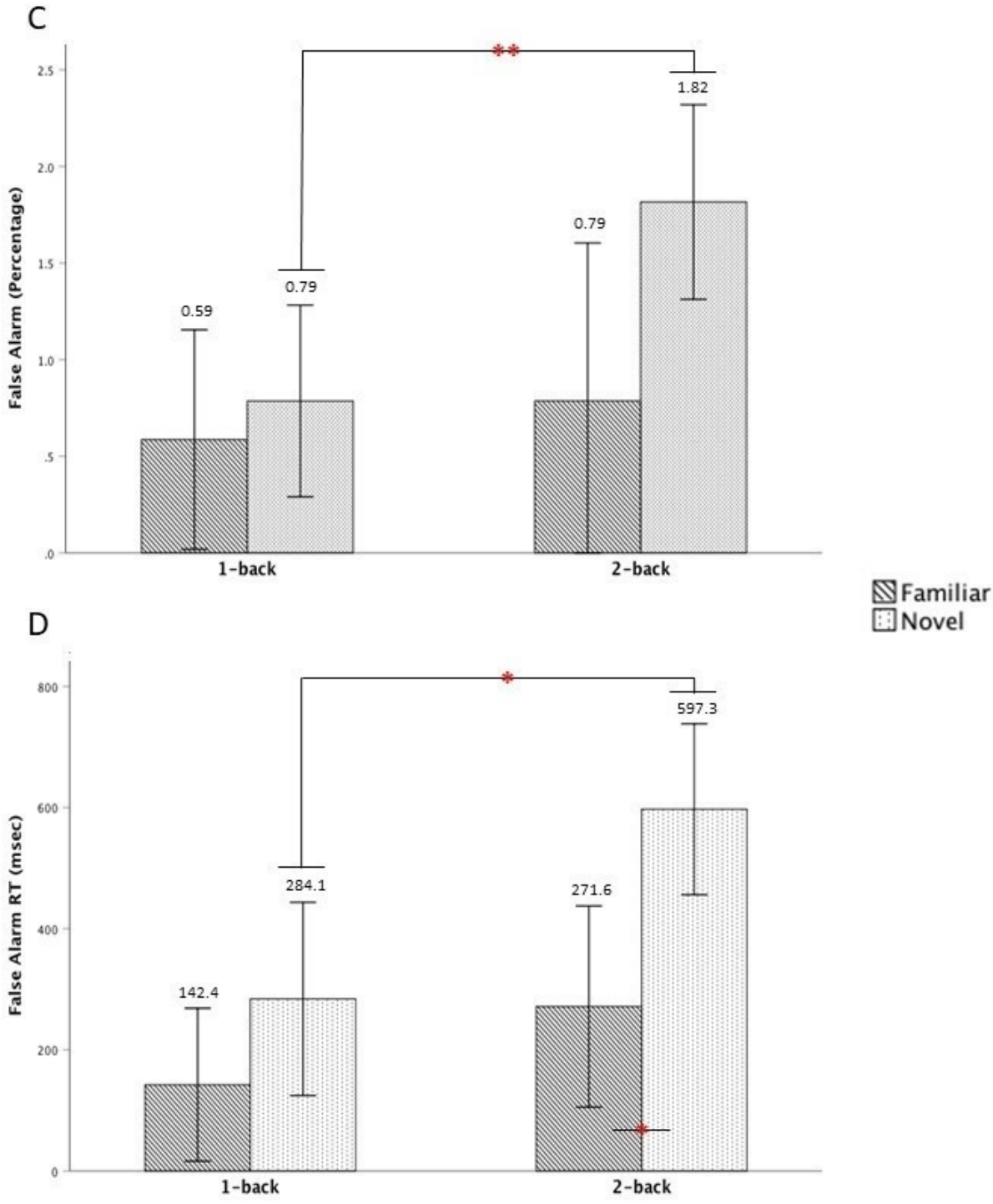
* F1 = familiar 1-back, F2 = familiar 2-back, N1 = novel 1-back, N2 = novel 2-back

Figure 3.1. Behavioral performance (accuracy and reaction time) for familiar and novel faces. **A)** Mean accuracy for 1-back and 2-back tasks, **B)** Mean hit reaction time for 1-back and 2-back tasks.



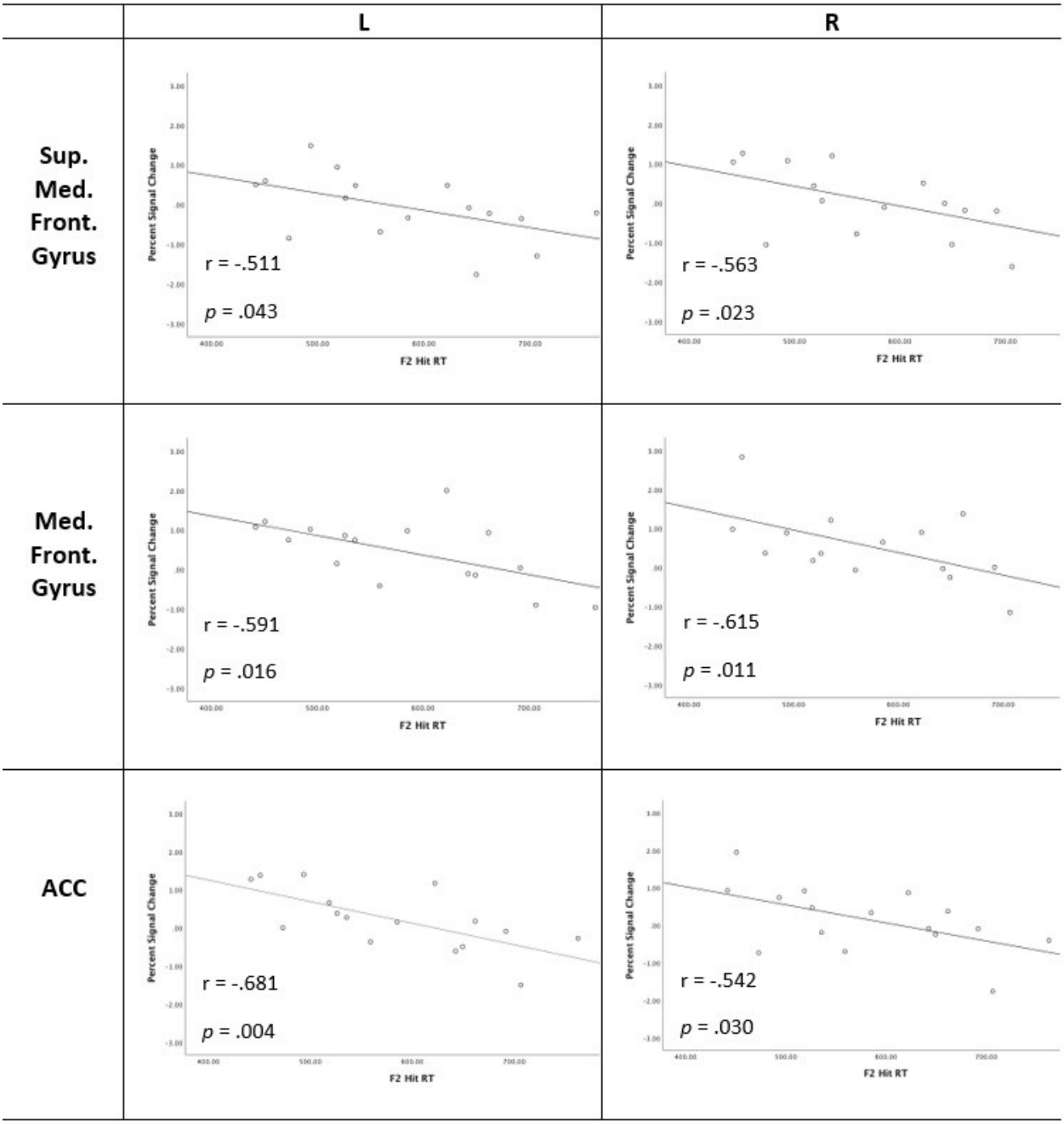
* denotes p < .05. ** denotes p < .01.

Figure 3.2. Behavioral performance (false alarm and reaction time) for familiar and novel faces. **C)** Mean false alarm for 1-back and 2-back tasks, **D)** Mean false alarm reaction time for 1-back and 2-back tasks.



* denotes p < .05. ** denotes p < .01.

Figure 3.3. ROI correlation graphs for reaction time for *Familiar 2-back > Novel 2-back* contrast.



*Sup. Med. Front. Gyrus = superior medial frontal gyrus, Med. Front. Gyrus = medial frontal gyrus, ACC = anterior cingulate cortex

Figure 3.4. ROI correlation graphs for hit accuracy and reaction time for *Familiar 1-back* > *Rest* (top) and *Novel 2-back* > *Rest* (bottom). Hit accuracy (left) and reaction time (right)

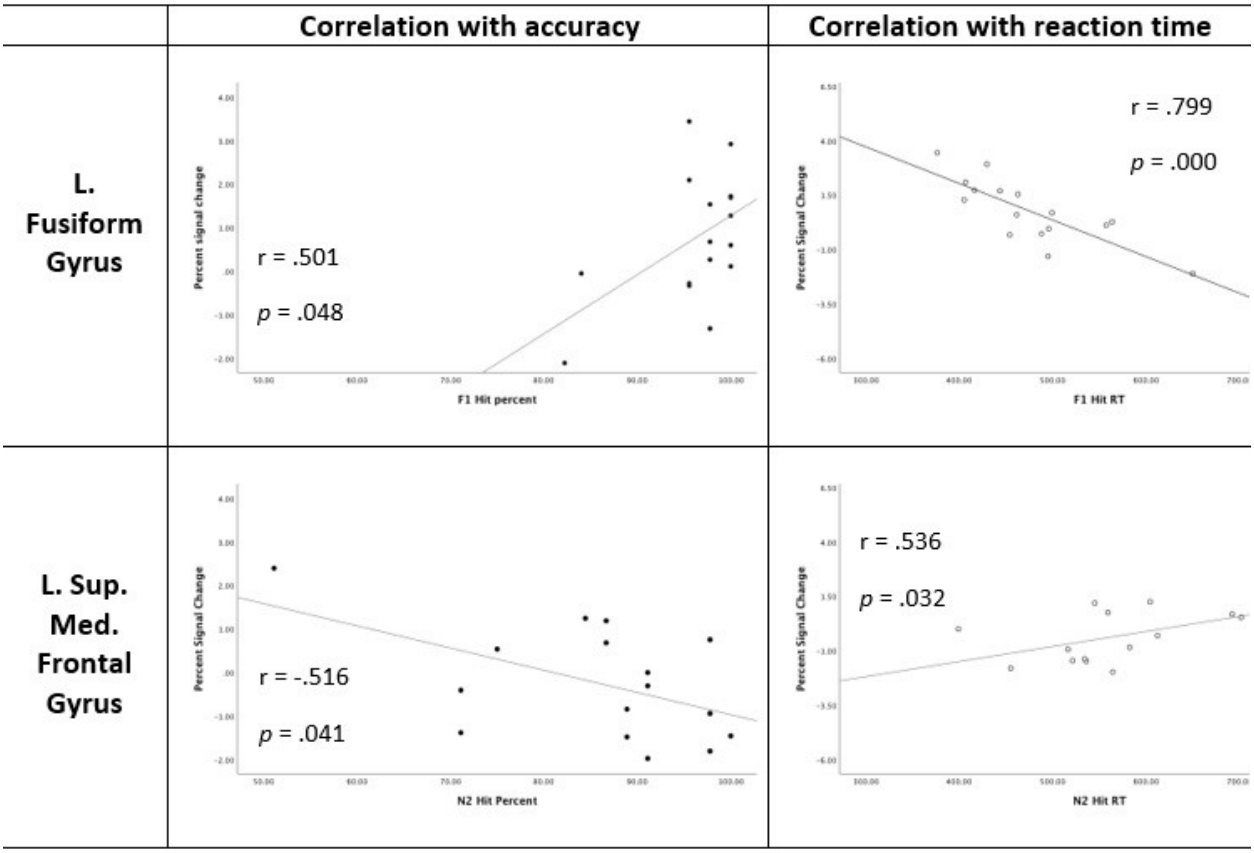


Figure 3.5. ROI correlation graphs for reaction time for *Novel 2-back > Rest*.

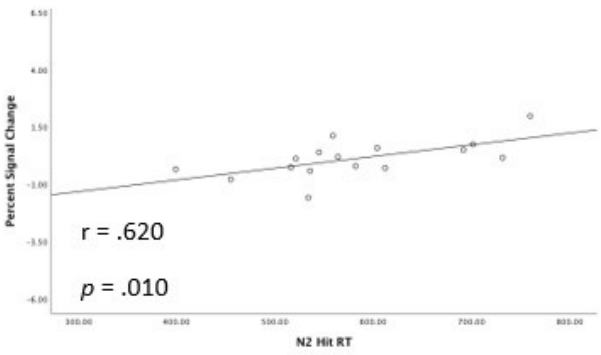
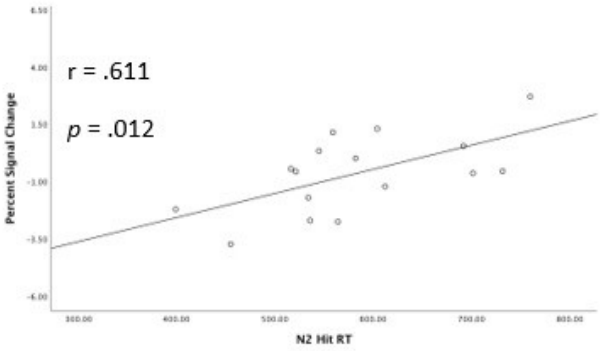
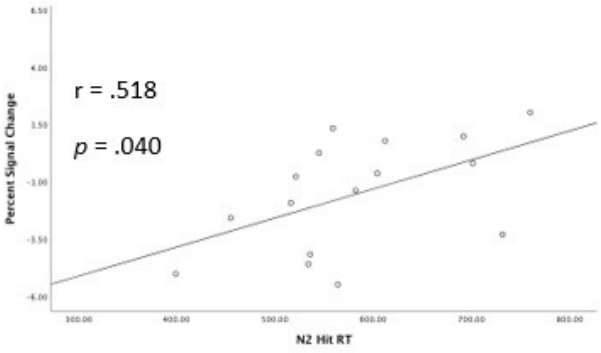
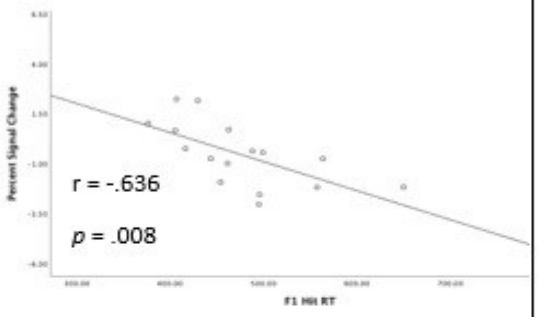
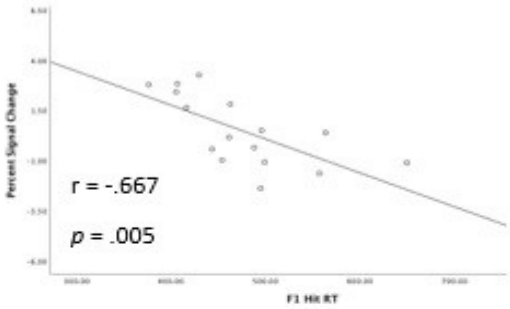
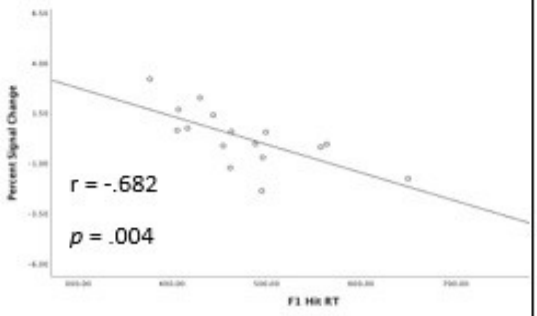
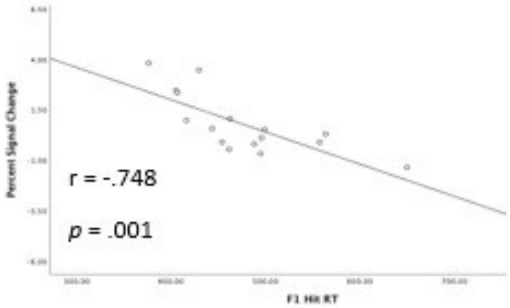
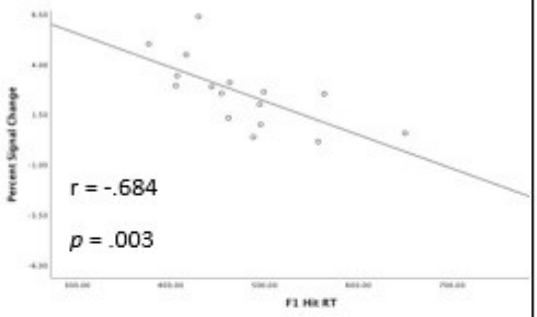
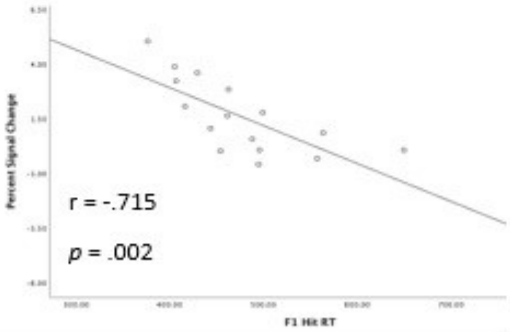
L. Superior Frontal Gyrus	
L. Anterior Cingulate Cortex	
L. Posterior Cingluate Cortex	

Figure 3.6. ROI correlation graphs for reaction time for *Familiar 1-back > Rest*.

	L	R
Sup. Occi. Gyrus		
Culmen		
Inf. Occi. Gyrus		
R. Fusiform Gyrus		

*Sup. Occi. Gyrus = superior occipital gyrus, Inf. Occi. Gyrus = inferior occipital gyrus

Figure 3.7. fMRI results for the main effect of working memory load. *2-back > 1-back* (blue) and *1-back > 2-back* (red). Top (saggital), middle (coronal), bottom (axial). Bar represents F contrast. 2-back activated the frontal and parietal regions, as well as insula, thalamus, and cerebellum. 1-back mainly activated the ventral stream, including temporal pole and hippocampus.

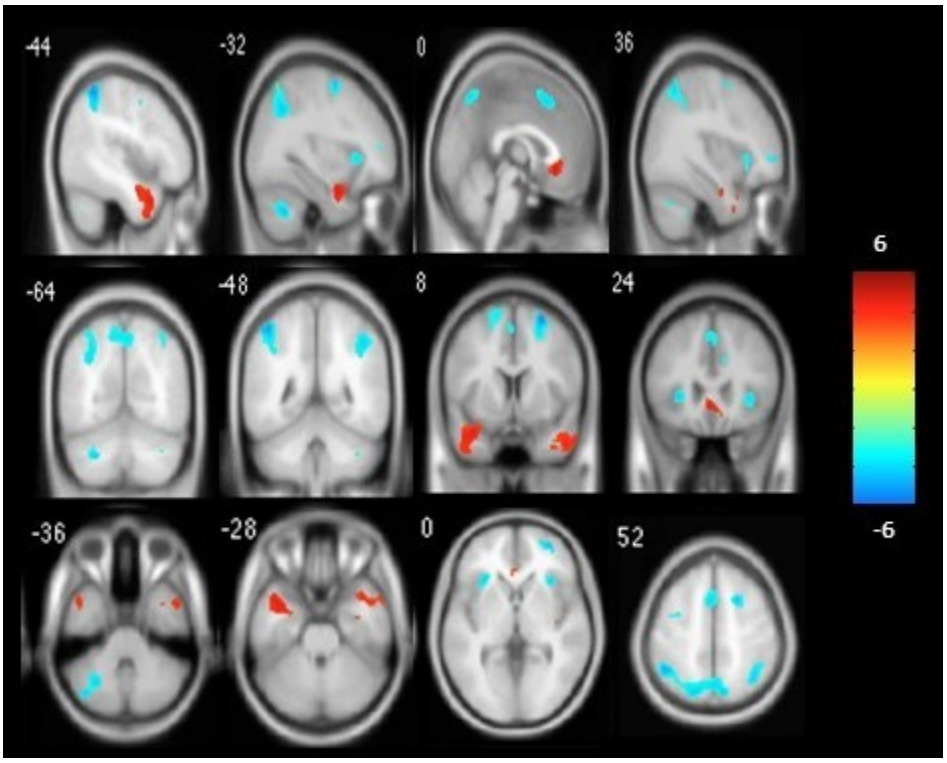


Figure 3.8. fMRI results for the main effect of familiarity. *Familiar > Novel* (yellow). Top (saggital), middle (coronal), bottom (axial). Bar represents F contrast. Only the anterior cingulate cortex was activated in resposne to familiar stimuli.

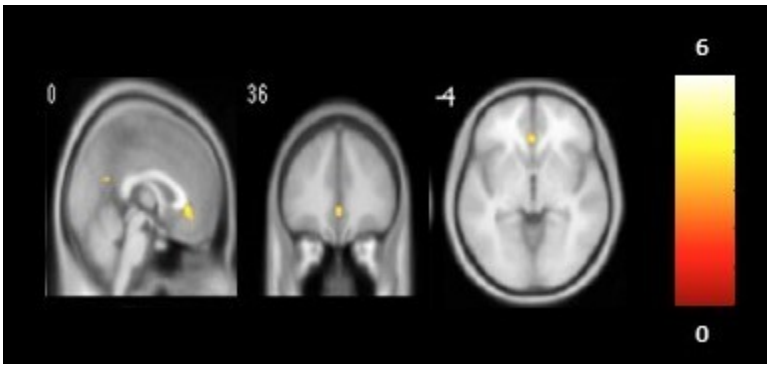


Figure 3.9. fMRI results for interaction effect of *Working memory load x Familiarity*. Top (saggital), middle (coronal), bottom (axial). Bar represents F contrast. Neural actiavtions were observed in frontal and temporal regions, as well as thalamus and cerebellum.

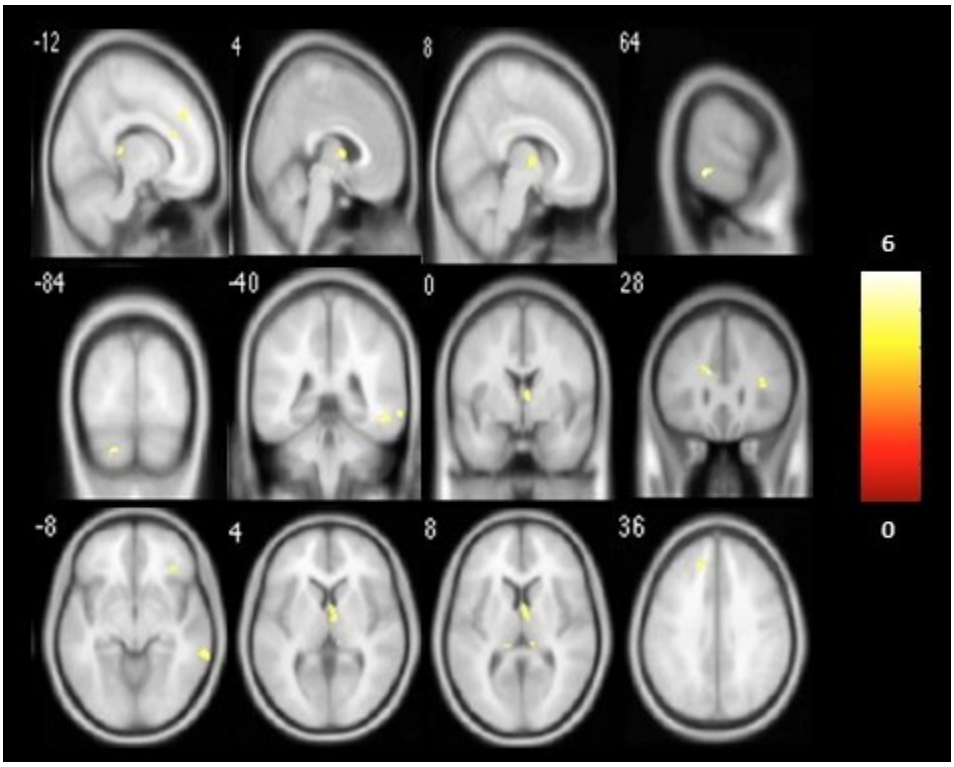


Figure 3.10. fMRI results for pairwise T contrast for *Familiar 2-back > Familiar 1-back*. Top (saggital), middle (coronal), bottom (axial). Bar represents T contrast. Neural activations were observed in the frontal and parietal regions, as well as the cerebellum.

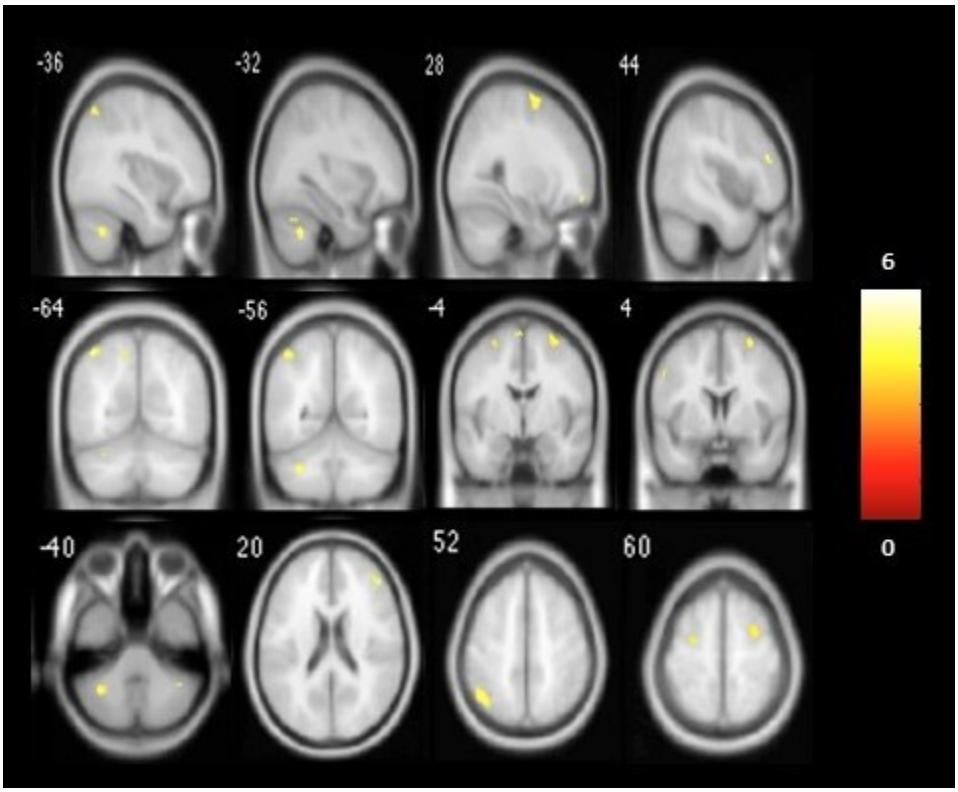


Figure 3.11. fMRI results for pairwise T contrast for *Novel 2-back > Novel 1-back*. Top (saggital), middle (coronal), bottom (axial). Bar represents T contrast. Neural actiavtions were observed in the frontal and parietal regions, as well as insula and thalamus.

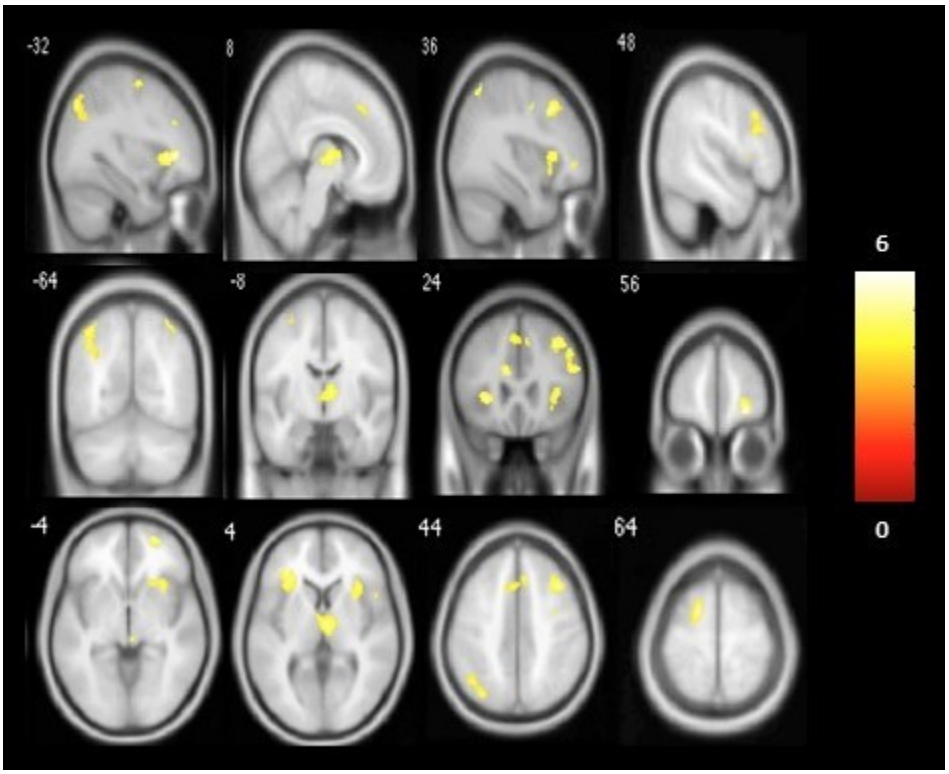
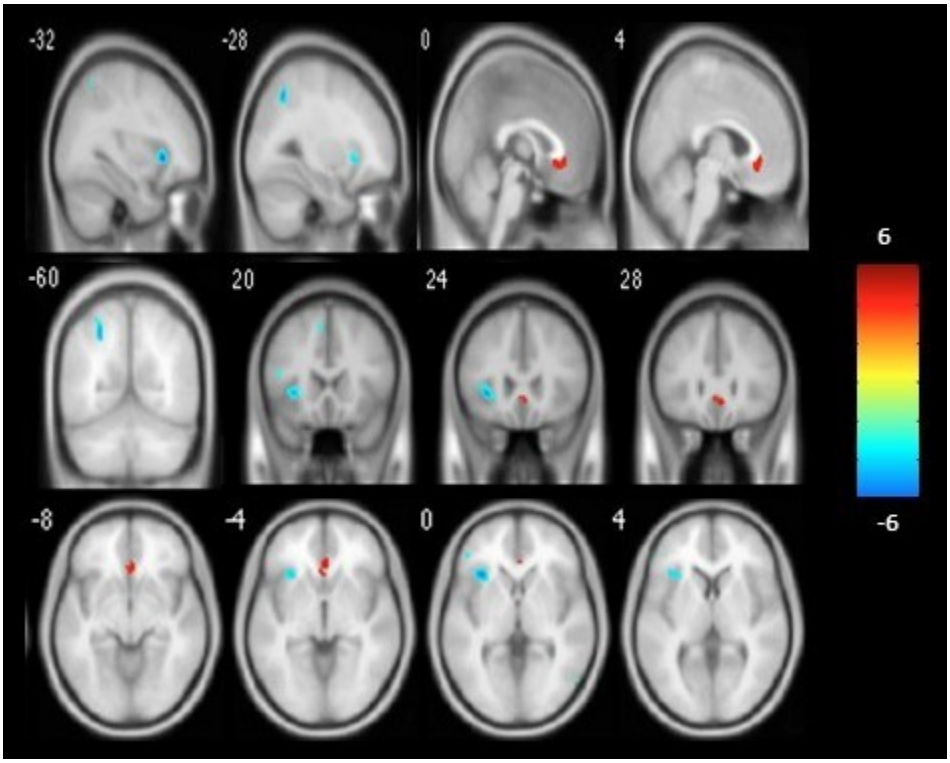


Figure 3.12. fMRI results for pairwise T contrast for Novel 2-back > Familiar 2-back and Familiar 2-back > Novel 2-back. Top (saggital), middle (coronal), bottom (axial). Bar represents T contrast. *Novel 2-back > Familiar 2-back* (blue) and *Familiar 2-back > Novel 2-back* (red). Familiar 2-back only activated the right anterior cingulate cortex, whereas Novel 2-back activated the frontal and parietal regions.



APPENDIX B TABLES

Table 2.1. Complete list of brain regions selected for ROI analysis.

	ROI	Hem
1.	Superior Medial Frontal Gyrus	L and R
2.	Superior Frontal Gyrus	L and R
3.	Middle Frontal Gyrus	L and R
4.	Inferior Frontal Gyrus	L and R
5.	Medial Frontal Gyrus	L and R
6.	Inferior Parietal Lobule	L and R
7.	Precuneus	L and R
8.	Middle Temporal Gyrus	L and R
9.	Inferior Temporal Gyrus	L and R
10.	Parahippocampus	L and R
11.	Fusiform Gyrus	L and R
12.	Superior Occipital Gyrus	L and R
13.	Middle Occipital Gyrus	L and R
14.	Inferior Occipital Gyrus	L and R
15.	Culmen	L and R
16.	Anterior Cingulate Cortex	L and R
17.	Posterior Cingulate Cortex	L and R
18.	Thalamus	L and R
19.	Insula	L and R
20.	Cerebellum (crus 1)	L and R
21.	Cerebellum (crus 2)	L and R

Table 3.1 Demographic information for all study subjects.

Number	Subject	Gender	Age	Highest Education Level	Years of Education since Grade 1
3	TD	M	23	Degree holder	17
4	TS	M	21	Undergraduate	16
5	ZS	M	19	Undergraduate	13
6	AS	F	22	High school diploma	12
7	AL	F	19	Undergraduate	14
8	SL	F	20	Undergraduate	14
9	HA	M	19	Undergraduate	15
11	JP	F	20	Undergraduate	14
12	SF	F	25	High school diploma	12
13	TP	M	19	Undergraduate	13
14	KM	F	18	Undergraduate	13
15	SJ	F	19	Undergraduate	14
16	TL	F	20	Undergraduate	14
17	SJ	F	21	Undergraduate	17
18	JG	M	21	Undergraduate	13
19	NB	M	20	Undergraduate	15

Table 3.2. Behavioural Performance (N=16) for face working memory n-back task.

	Mean Accuracy ± SD	Accuracy RT ± SD	Mean False Alarm ± SD	False Alarm RT ± SD
1-back				
Familiar	96.22% (± *5.43*)	475.3ms (± *69.9*)	0.59% (± *1.13*)	142.4ms (± *252.6)*
Novel	97.78% (± *3.44*)	486.2ms (± *72.0*)	0.79% (± *0.99*)	284.1ms (± *318.9*)
2-back				
Familiar	92.25% (± *6.96*)	582.7ms (± *97.6*)	0.79% (± *1.63*)	271.6ms (± *332.2*)
Novel	85.66% (± *12.88*)	582.1ms (± *98.7*)	1.82% (± *1.01*)	597.3ms (± *282.6*)

Table 3.3. Main and interaction effects of sustained brain activity. p=.001, T=11.973, voxel size threshold >5, x, y, z are peak coordinates of each cluster.

	Brain region	Hem	BA	Cluster voxels	x	y	z	F
	Main Effect (2-back > 1-back)							
Frontal Lobe	Superior Frontal Gyrus	R	6	393	30	4	62	5.8386
	Middle Frontal Gyrus	L	10	12	-32	50	10	3.4991
		R	11	110	32	58	0	4.3426
	Precentral Gyrus	L	6	346	-32	-2	60	4.4632
	Supplementary Motor Area	L	32	248	-2	20	46	4.1576
Parietal Lobe	Inferior Parietal Lobule	L	40	1302	-44	-54	56	5.2997
		R	40	414	42	-50	48	4.245
Subcortical	Insula	L	47	73	-30	24	2	4.2849
		R	47	76	34	24	2	4.0278
	Thalamus	R		39	6	-10	8	3.5991
	Midcingulate Cortex	R		32	12	22	30	3.4598
Cerebellum	Cerebellum (Crus 1)	L		176	-30	-62	-38	4.437
		R		9	36	-64	-34	3.6248
	Cerebellum 8	L		5	-34	-52	-50	3.4704
	Main Effect (1-back > 2-back)							
Temporal Lobe	Middle Temporal Pole	R	21	269	50	8	-34	4.1895
	Hippocampus	R	20	91	30	-22	-16	4.387
	Parahippocampal Gyrus	L	30	10	-26	-16	-24	3.3724
	Rolandic Operculum	R	48	10	54	-12	18	3.3906
Subcortical	Anterior Cingulate Cortex	L	11	161	-2	28	-6	4.9338
	Insula	R	48	26	42	-16	-2	3.5087
	Main Effect of Familiarity (familiar > novel)							
Subcortical	Anterior Cingulate Cortex	R	11	26	0	32	-4	16.3441
	Interaction Effect							
Frontal Lobe	Superior Frontal Gyrus	L	32	41	-14	36	34	5.6138
	Inferior Frontal Gyrus	R	47	13	38	34	-6	4.7503
	Medial Frontal Gyrus	R	10	9	14	60	-2	4.4294
Temporal Lobe	Inferior Temporal Gyrus	R	20	39	66	-42	-10	5.7444
	Parahippocampal Gyrus	L	20	9	-28	-18	-22	4.4353
Subcortical	Thalamus	L		11	-16	-8	0	5.463
		R		19	12	-30	6	5.163
Cerebellum	Cerebellum (Crus 2)	L		6	-18	-84	-36	5.7581

Table 3.4. T contrast of working memory load in familiar and novel face conditions, as well as T contrast of familiarity in high working memory load. Working memory load (above two) and familiarity (bottom two) contrast. p=.001, T=3.7328, voxels size threshold >5, x, y, z are peak coordinates of each cluster.

	Brain region	Hem	BA	Cluster voxels	x	y	z	T
	Novel 2-back > 1-back							
Frontal Lobe	Superior Frontal Gyrus	R	11	87	26	58	-8	5.7397
	Middle Frontal Gyrus	L	45	25	-40	42	16	4.8886
		R	8	45	22	14	50	4.2823
	Inferior Frontal Gyrus	L	47	195	-32	36	4	6.0815
		R	45	357	54	28	24	5.5559
	Supplementary Motor Area	L	6	139	-16	2	64	5.5487
	Precentral Gyrus	L	6	31	-32	-6	60	4.1969
Parietal Lobe	Superior Parietal Lobule	R	7	37	36	-62	58	4.6119
	Inferior Parietal Lobule	L	39	406	-44	-60	50	4.6388
Subcortical	Thalamus	L		13	-14	-12	-2	4.137
		R		285	4	-12	4	5.0866
	Familiar 2-back > 1-back							
Frontal Lobe	Superior Frontal Gyrus	L	6	15	-26	-6	60	4.1439
		R	6	68	30	-2	64	4.8067
	Middle Frontal Gyrus	R	45	25	44	40	22	5.0708
	Precentral Gyrus	L	6	11	-52	2	40	4.2665
	Supplementary Motor Area	L	6	12	-4	-6	68	4.346
Parietal Lobe	Inferior Parietal Lobule	L	7	97	-40	-62	56	5.4994
	Precuneus	L	7	16	-12	-66	48	4.2331
Cerebellum	Cerebellum (Crus 1)	L		49	-34	-58	-38	4.9629
	Cerebellum (Crus 2)	R		7	42	-50	-40	4.8582
	Cerebellum 6	L		5	-32	-64	-28	3.984
	Novel 2-back > Familiar 2-back							
Frontal Lobe	Inferior Frontal Gyrus	L		16	-44	44	-14	4.2397
	Supplementary Motor Area	L	6	25	-8	16	56	4.2604
Parietal Lobe	Superior Parietal Lobule	L	7	66	-28	-62	48	5.9956
Subcortical	Insula	L	47	104	-32	22	-2	6.7122
	Familiar 2-back > Novel 2-back							
Subcortical	Anterior Cingulate Cortex	R	11	74	2	28	-8	4.5262

Table 3.5. Attention-related T contrast in familiar and novel face conditions, as well as T contrast of familiarity in low working memory load. Attention-related (above two) and familiarity (bottom) contrast. p=.001, T=3.7328, voxels size threshold >5, x, y, z are peak coordinates of each cluster.

	Brain region	Hem	BA	Cluster voxels	x	y	z	T
	Novel 1-back > 2-back							
Temporal Lobe	Superior Temporal Gyrus	L	48	34	-40	-2	-14	4.3302
		R		151	44	-6	-8	5.6004
	Superior Temporal Pole	L	38	83	-36	6	-22	4.5118
	Middle Temporal Pole	R	20	84	40	8	-34	5.1537
	Hippocampus	R	20	45	32	-22	-16	5.1018
	Fusiform Gyrus	L	20	7	-32	-28	-16	4.015
	Rolandic Operculum	L	48	7	-46	-16	14	4.1481
		R	48	29	64	0	10	4.2464
Subcortical	Olfactory	R	11	12	8	24	-12	4.4526
	Anterior Cingulate Cortex	L	11	39	-2	28	-8	5.7196
	Familiar 1-back > 2-back							
Frontal Lobe	Superior Medial Frontal Gyrus	L	32	48	0	52	14	4.2918
	Superior Frontal Gyrus	L	32	11	-12	38	42	3.966
	Inferior Frontal Gyrus	L	38	27	-42	30	-18	4.4335
		R	47	17	28	28	-14	4.3405
Temporal Lobe	Superior Temporal Gyrus	R	22	8	68	-28	10	3.9935
	MIddle Temporal Gyrus	L	22	83	-58	-20	-4	6.6845
	Parahippocampal Gyrus	L	30	724	-26	-18	-24	6.0383
		R	20	70	34	-26	-16	4.6862
	Fusiform Gyrus	L	37	16	-24	-40	-20	4.5176
Occipital Lobe	Superior Occipital Gyrus	R	17	28	20	-96	16	5.1051
	Middle Occipital Gyrus	R		21	30	-90	20	4.8657
	Inferior Occipital Gyrus	R	18	34	34	-92	-8	4.4556
	Calcarine Sulcus	L	17	71	-4	-62	12	5.1766
Subcortical	Anterior Cingulate Cortex	L	32	80	-8	44	8	4.5514
	Midcingulate Cortex	L		14	-12	-18	44	4.106
	Familiar 1-back > Novel 1-back							
Frontal Lobe	Superior Medial Frontal Gyrus	L	32	98	-4	46	20	5.1903
		R	32	5	8	52	26	4.0619
	Superior Frontal Gyrus	L	32	17	-14	40	40	4.4789
	Medial Frontal Gyrus	L	11	12	-8	44	-10	4.0197
	Middle Frontal Gyrus	R	9	13	22	30	38	4.2042
Temporal Lobe	Rolandic Operculum	R	48	10	40	-16	18	4.1665

Parietal Lobe	Inferior Parietal Lobule	L	2	18	-56	-26	48	4.4907
Occipital Lobe	Superior Occipital Gyrus	L	17	15	-10	-94	4	4.6479
	Middle Occipital Gyrus	L	39	74	-36	-66	28	4.765
	Cuneus	R	18	5	10	-94	16	4.2037
Subcortical	Thalamus	R		62	14	-20	14	4.8142
	Insula	R	48	39	40	-2	4	4.5633
	Midcingulate Cortex	L		57	-6	-16	46	5.6631
		R	23	17	2	-36	34	4.1053
Cerebellum	Cerebellum (Crus 1)	R		47	28	-72	-38	5.0784
	Cerebellum 8	L		20	-30	-44	-50	6.6856

Table 3.6. T contrast of *Scramble > Rest*. p=.001, T=3.7328, voxels size threshold >5, x, y, z are peak coordinates of each cluster.

	Brain region	Hem	BA	Cluster voxels	x	y	z	T
	Scramble > rest							
Frontal Lobe	Superior Medial Frontal Gyrus	L	9	436	-4	46	38	5.4053
		R	9	26	12	42	46	4.1792
	Superior Frontal Gyrus	L	11	25	-18	54	-12	4.4101
	Middle Frontal Gyrus	L	8	92	-34	4	56	4.6462
		R	46	11	50	46	-8	4.1276
	Inferior Frontal Gyrus	L	48	1071	-46	24	20	6.4173
		R	44	1323	56	22	24	6.3705
	Supplementary Motor Area	L		32	0	10	56	4.1362
Temporal Lobe	Superior Temporal Pole	L		656	-36	26	-24	6.4012
		R	38	13	28	12	-26	4.0811
	MIddle Temporal Gyrus	L	39	7	-40	-68	18	4.2312
Parietal Lobe	Superior Parietal Lobule	L	7	6	-26	-62	42	3.8822
		R	7	187	32	-60	62	4.507
Occipital Lobe	Middle Occipital Gyrus	L	19	81	-28	-76	26	5.3661
	Inferior Occipital Gyrus	L	18	3982	-26	-90	-6	9.5665
		R	19	6012	38	-84	-10	9.5072

Table 3.7. ROI correlation table for *Familiar 2-back > Novel 2-back* contrast for both hit accuracy and reaction time.

Regions of Interest	Hem	Accuracy Correlation (sig.)	RT Correlation (sig.)
Superior Medial Frontal Gyrus	L		-0.511 (0.043*)
	R		-0.563 (0.023*)
Medial Frontal Gyrus	L		-0.591 (0.016*)
	R		-0.615 (0.011*)
Inferior Frontal Gyrus	L	0.629 (0.009**)	
	R		-0.549 (0.028*)
Middle Temporal Gyrus	L	0.568 (0.022*)	
Fusiform	L	0.549 (0.028*)	
	R	0.526 (0.036*)	
Parahippocampus	L		-0.501 (0.048*)
Superior Occipital Gyrus	L	0.712 (0.002**)	
Middle Occipital Gyrus	L	0.531 (0.034*)	
	R		-0.588 (0.017*)
Inferior Occipital Gyrus	L	0.598 (0.014*)	-0.528 (0.035*)
Anterior Cingulate Cortex	L		-0.681 (0.004**)
	R		-0.542 (0.030*)

* denotes $p < .05$. ** denotes $p < .01$

Table 3.8. ROI correlation table for hit accuracy vs. baseline (rest) contrast for F1, F2, N1, and N2 condition.

Regions of Interest	Hem	F1 corr. (sig.)	F2 corr. (sig.)	N1 corr. (sig.)	N2 corr. (sig.)
Superior Medial Frontal Gyrus	L				-0.516 (0.041*)
Inferior Frontal Gyrus	L		0.499 (0.049*)		
	R		0.548 (0.028*)		
Middle Temporal Gyrus	R			0.552 (0.027*)	
Inferior Temporal Gyrus	L		0.527 (0.036*)		
	R		0.659 (0.005**)		
Fusiform	L	0.501 (0.048*)	0.591 (0.016*)		
	R		0.529 (0.035*)		
Parahippocampus	R		0.528 (0.035*)	0.524 (0.037*)	
Superior Occipital Gyrus	R		0.519 (0.039*)		
Inferior Occipital Gyrus	L		0.728 (0.001**)		
Culmen	R		0.498 (0.050*)		
Insula	L		0.537 (0.032*)		
	R		0.595 (0.015*)		
Cerebellum (crus 1)	L		0.566 (0.022*)		

F1 = familiar 1-back, F2 = familiar 2-back, N1 = novel 1-back, N2 = novel 2-back, corr. = correlation, sig. = p value significance
* denotes $p < .05$. ** denotes $p < .01$

Table 3.9. ROI correlation table for the hit reaction time vs. baseline (rest) contrast for F1 and N2 condition.

Regions of Interest	Hem	F1 corr. (sig.)	N2 corr. (sig.)
Superior Medial Frontal Gyrus	L		0.536 (0.032*)
Superior Frontal Gyrus	L		0.620 (0.010*)
Middle Frontal Gyrus	L		0.514 (0.042*)
Precuneus	R	-0.518 (0.040*)	
Middle Temporal Gyrus	L	-0.543 (0.030*)	
Inferior Temporal Gyrus	L	-0.523 (0.038*)	
Fusiform	L	-0.799 (0.000**)	
	R	-0.715 (0.002**)	
Parahippocampus	L	-0.552 (0.027*)	
	R	-0.683 (0.004**)	
Superior Occipital Gyrus	L	-0.636 (0.008**)	
	R	-0.667 (0.005**)	
Middle Occipital Gyrus	L	-0.633 (0.009**)	
	R	-0.555 (0.026*)	
Inferior Occipital Gyrus	L	-0.684 (0.003**)	
Culmen	L	-0.682 (0.004**)	
	R	-0.748 (0.001**)	
Anterior Cingulate Cortex	L		0.611 (0.012*)
Posterior Cingulate Cortex	L	-0.589 (0.016*)	0.518 (0.040*)
Thalamus	R	-0.621 (0.010*)	
Cerebellum (crus 1)	L	-0.612 (0.012*)	

F1 = familiar 1-back, N2 = novel 2-back, corr. = correlation, sig. = p value significance
* denotes $p < .05$. ** denotes $p < .01$

APPENDIX C INFORMATION SHEET AND PARTICIPANT CONSENT FORM

Form C1

Title of Study: Neural basis of auditory working memory and executive function

Principle Investigator: Dr. Ada Leung, Assistant Professor

Address: 2-12 Corbett Hall, Department of Occupational Therapy
Faculty of Rehabilitation Medicine
University of Alberta
Edmonton, AB, T6G2G4
Email: ada.leung@ualberta.ca
Phone: (780) 492-2342

Why am I being asked to take part in this research study?
This study investigates cognitive profiles and brain activities associated with working memory training and behavioral improvements, particularly cognitive functions, after the training. This study will help us better understand the cognitive mechanisms and neural systems about executive function and working memory, which will help us in the design of rehabilitation programs for people with brain damage.

Before you make a decision on whether to consent to take part in the study, the researcher will go over this consent form with you. You are encouraged to ask questions if you feel anything needs to be made clearer. You will be given a copy of this form for your records.
Your participation is voluntary. There are three parts: (1) baseline testing of cognitive profile; (2) cognitive training and pre- and post-training testing of cognitive profile; and (3) functional magnetic resonance imaging (MFI) before and after the cognitive training. You will be screened and assigned to perform in one or all of the parts.

There are some criteria for being in this study and you will be screened for the suitability to be in this study as a participant. In the screening procedure, you will be required to fill out an intake form which will gather some demographic information such as your age, sex, education, and history of neurological or psychological illness. If you opt to perform functional MRI, then you will have to fill in a magnetic resonance imaging (MRI) screening questionnaire so that we can decide if you are physically fit to undergo MRI procedure. We may also ask you to provide 12 photos of your significant others so that we can assess how your brain process familiar information in working memory before and after the working memory training. You are encouraged to ask questions if you feel anything needs to be made clearer when time comes for you to fill in these two questionnaires.

What is the reason for doing the study?
The reason for doing this study is because it is still unclear about how our brain responds to cognitive training and the types of cognitive skills that can be improved with cognitive training. This study aims to investigate specifically how our brain activates after a course of working memory training and determines the changes of executive functions, e.g., how well we organize information and make decisions, and how fast we process information, after the training. We will look at your brain activities and behavioral performance on a variety of cognitive tasks, e.g., working memory, response inhibition, and attention, before and after the training. The scientific data obtained from this study will provide important information for us to design rehabilitation training programs and remedial activities for people with brain injuries.

What will I be asked to do?
For those who participate in part 1 (i.e., cognitive profile):
You will be asked to perform a series of cognitive tests which measure attention, memory and executive function. These tests are paper-and-pencil tests and and/or computer tasks. You will be given rest breaks in between tests. You will need about 2.5 hours to complete all tests.

For those who participate in part 2 (i.e., cognitive training):
You will be asked to participate for a consecutive of four to eight weeks, from Monday to Friday, each day for 1.5 hours. The training will be done at home. We will help you install the computer program on your computer. We will also ask for your help to send us your response file every day after completing the task via email. For the training, you will be randomly assigned to participate in either the visual working memory training group, the auditory working memory training group, the control group for visual working memory training or the control group for auditory working memory training. During randomization, you will be asked to pick a card from a bag of cards. The cards are marked with one of four symbols which will tell whether you are in the training or the control group. You will not be told about the group you are in but the researcher will know the group from the symbol and will tell you clearly the tasks that you are going to do in the session during the training period. In addition, we may ask you to give us 12 photos of your significant others if you are in the visual working memory training group. This will allow us to assess how your brain processes familiar information in working memory before and after the visual working memory training.

For those who participate in part 3 (i.e., functional MRI)
The photos you provided will be used as your familiar face images and as unfamiliar face images of one other participant. The photos will be coded by numbers and there will not be any identification information attached to the photos. The photos will be edited by one research assistant in the laboratory so that the photos will be gray scale and contain only the hair and the face. The photos will be used in the working memory paradigm during functional magnetic resonance imaging (fMRI) before and after the working memory training. The photos will only be used for data collection during the fMRI procedure. Once the data collection procedure is over, the photos will be deleted permanently from the computer in the MRI centre as well as the computer in the laboratory. Only two participants will view one set of photos. That means one participant will perceive the photos as familiar

faces and the other participant will perceive the same set of photos as unfamiliar faces. The photos will not be kept in any forms in any computer. The purpose of this part of the testing is to identify the neural mechanisms in processing familiar information in working memory after a course of working memory training using commonly used digits and letters.

Confidential handling of photos (where applicable):
The photos will not be shared among researchers. Only one research assistant will edit the photos. The photos and images will all be coded by numbers and none of the photos will be identified by the third person. That is, only the participant who provides the photos and the research assistant working on the photos can identify the photos or images. During the experiment, the photos will be viewed only by the participant who provided the photos (as familiar face images) and another participant (as unfamiliar or novel face images). Also, the photos will be immediately and permanently deleted from the computers in the MRI centre and the laboratory once when the data collection from the two participants is over. In addition, the research assistant will edit the photos in the laboratory to maintain confidentially.

Procedures:
All behavioral testing, including administration of cognitive tests, will take place in the Functional and Cognitive Neuroscience Laboratory at the Faculty of Rehabilitation Medicine, University of Alberta (Corbett Hall Room 1-48). In situation where physical presence at the laboratory is difficult, the administration of cognitive tests will be administered by a research assistant at a quiet room convenient to the participant.

For the cognitive training and functional MRI scanning, the first session will take place in the Functional and Cognitive Neuroscience Laboratory at the Faculty of Rehabilitation Medicine, University of Alberta, where you will be explained in more detail about the MRI procedure and screened for safety to perform MRI, as well as to complete some cognitive tests. You will learn the working memory tasks. After that, you will come to the Peter S. Allen MR Research Centre at the University of Alberta for MRI scanning. You will take part in the training at home. After the training, we will arrange another MRI session for you in order to assess your brain activity. Lastly, you will come to the Functional and Cognitive Neuroscience Laboratory to perform the cognitive tests that you have done in the first session.

What are the risks and discomforts?
The MRI scan is not associated with any known risks to your health and there is no evidence of short-term or long-term side effects. However, it is the policy of the Peter S. Allen MR Research Centre that if you are a woman of child-bearing age, that you not be pregnant at the time of the MRI scan. Prior to the MRI you will be required to fill out a questionnaire to ensure that there are no contraindications for performing the study. The only absolute requirements for the MRI scan are that you do **NOT** have an implanted cardiac pacemaker or any metal implants, pieces of shrapnel, aneurysm clips, or wires in your head.

Some more information about MRI scanning is provided to you as follows:

The MRI technique uses magnets and radiowaves to construct a picture of the brain on a computer. Before the scan begins, you will be asked to remove any magnetic metals that you may be wearing. You will be required to change your clothing and wear only a clean patient gown, provided in the Peter S. Allen MR Research Centre, during the MRI testing. You will be asked to lie on a padded bed that will be moved into a tunnel-like machine for the MRI scan of your brain. As you will be inside the machine during the scan, you may not be able to see the technicians or the investigators. However, there is an intercom system that will allow you to talk with them at any time. If you feel uncomfortable during the scan and you wish to discontinue the procedure, you can request to be taken out of the machine at anytime. This experiment requires that you be scanned two times, one before the working memory training, and one after the training. Each time will take approximately 1.5 hours. During the MRI scanning, you will be presented with a variety of auditory and visual tasks.

You should try to remain still as movement will blur the scan images. However, movement will not be dangerous to you in any way. You will hear moderately loud knocking or beeping during the scan while the MRI machine is in operation. You will be given ear plugs and a headphone to minimize the loud noise. Although you may find the noise to be unsettling, the machine cannot hurt you in any way.

There will be no risks associated with any cognitive tests / tasks except that you may feel tired with the training. However, you are given rest breaks during the tasks to alleviate fatigue.

It is not possible to know all of the risks that may happen in a study, but the researchers have taken all reasonable safeguards to minimize any known risks to a study participant.

If we find out anything new during the course of this research, particularly from the MRI scan images of your brain, which may change your willingness to be in the study, we will tell you about these findings.

What will you need to do?
Your responsibility on the experiment is to pay full effort when performing cognitive tests, cognitive training, and tasks in the MRI scanner. You will need to press buttons when performing cognitive tasks during the testing, training, and MRI scanning.

What are the benefits to me?
This study has no direct benefits to you. You are not expected to get any benefit from being in this research study. However, the result of this study will help the advancement of knowledge and help us understand the neural basis of executive function and working memory, which will be useful for rehabilitation for people with brain damage in the future. If you are interested, we will provide you with the final results of the study when they appear in press.

What happens if I am injured because of this research?
If you are injured as a result of being in this study, you will receive necessary medical treatment, at no additional cost to you. By signing this consent form you are not releasing the investigator(s), institution(s) and/or sponsor(s) from their legal and professional responsibilities.

Do I have to take part in the study?
Your participation is voluntary and being in this study is your choice. If you decide to be in the study, you can change your mind and stop being in the study at any time. No one will be angry with you if you decide you don't want to continue in this study, or if you decide to stop part ways through. If you withdraw, we will continue to use the data we have collected. The data will be stored for a minimum of 5 years. If you do not want us to use your data then the data will no longer be used in the study, but it will still be stored for a minimum of 5 years.

What will it cost me to participate?
There is no cost for you to participate in this experiment.

Will I be paid to be in the research?
For those who participate in parts 2 and 3 (i.e., cognitive training and functional MRI), you will be reimbursed for public transportation (i.e., ETS) round trip fare for coming to the Functional and Cognitive Neuroscience Laboratory and the Peter S. Allen MR Research Centre. We will do so by giving you ETS tickets after your ride. Upon successful completion of the experiment, you will receive a $40 gift card for use in a local restaurant as an appreciation for your participation. The reward is given to you only after successful completion of the experiment. If you withdraw from the study after successful completion of the first week you will receive a $20 gift card.

Will my information be kept private?
Your information and your results are confidential. Neither your identity nor any personal information will be available to anyone other than the investigators. No personal information will be disclosed in any resulting publication or presentation. If any unexpected medical findings should arise from the results of the MRI procedure involved in this project, we will recommend that you have a follow-up health assessment at your choice and we will provide all relevant information to the physician that you specify.

During the study we will be collecting demographic and health data about you. We will do everything we can to make sure that this data is kept private. No data relating to this study that includes your name will be released outside of the laboratory and the Peter S. Allen MR Research Centre or published by the researchers. Sometimes, by law, we may have to release your information with your name so we cannot guarantee absolute privacy.

However, we will make every effort to make sure that all your information is kept private.

This research study will be used in thesis / dissertation, research articles, presentations, and teaching. However, none of the participants' information will be released and no participant will be personally identified in any of these.

At the University of Alberta, we keep data stored for 5 years after the end of the study. If you leave the study and do not wish your data to be used then your data will no longer be used in the study, but it will still be stored for a minimum of 5 years.

There is a possibility that your data will be used in future unspecified research projects. However, this must first be approved by a Research Ethics Board.

What if I have questions?
If you have any questions about the research now or later, please do not hesitate to contact Dr. Ada Leung at (780) 492-2342. For emergency contact after office hours, please use (780) 439-6585.

If you have any questions regarding your rights as a research participant, you may contact the Research Ethics Office at (780) 492-2615. This office has no affiliation with the study investigators.

There is no actual or potential conflicts of interest with respect to remuneration received from the funding agency for conducting or being involved with any part of the study and/or the possibility of commercialization of research findings. This study is sponsored by the Department of Occupational Therapy at the Faculty of Rehabilitation Medicine to the principle investigator.

Further information
The plan for this study has been reviewed for its adherence to ethical guidelines by a Research Ethics Board at the University of Alberta. For questions regarding participant rights and ethical conduct of research, please contact the Research Ethics Office at (780) 492-2615.

CONSENT

Form C2

Title of Study: Neural basis of executive function and working memory

Principal Investigator: Dr. Ada Leung **Phone Number:** (780)-492-2342

Address: 2-12 Corbett Hall, Department of Occupational Therapy
Faculty of Rehabilitation Medicine, University of Alberta, Edmonton, AB, T6G2G4
Email: ada.leung@ualberta.ca

	Yes	No
Do you understand that you have been asked to be in a research study?	☐	☐
Have you read and received a copy of the attached Information Sheet?	☐	☐
Do you understand the benefits and risks involved in taking part in this research study?	☐	☐
Have you had an opportunity to ask questions and discuss this study?	☐	☐
Do you understand that you are free to leave the study at any time, without having to give a reason and without any penalty on you?	☐	☐
Has the issue of confidentiality been explained to you?	☐	☐
Do you understand who will have access to your data, including personally identifiable health information and MRI scans?	☐	☐

I agree to participate in ☐ Part 1 (cognitive profile); ☐ Part 2 (cognitive training); and/or ☐ Part 3 (functional MRI) **of this study. (Please tick the box applicable to you)**

Signature of Research Participant_____

(Printed Name)_____

Date:_____

I believe that the person signing this form understands what is involved in the study and voluntarily agrees to participate.

Signature of Investigator or Designee_____ **Date:**_____

(Printed Name)_____

THE INFORMATION SHEET MUST BE ATTACHED TO THIS CONSENT FORM AND A COPY GIVEN TO THE RESEARCH PARTICIPANT

APPENDIX D INTAKE FORM

Title of Study: Neural basis of auditory working memory and executive function

Principle Investigator:
Name: Dr. Ada Leung, Assistant Professor
Address: 2-12 Corbett Hall, Department of Occupational Therapy
Faculty of Rehabilitation Medicine
University of Alberta
Edmonton, AB, T6G2G4
Email: ada.leung@ualberta.ca
Phone: (780) 492-2342

Participant's code: _____

Part 1 – Personal Information
The following personal information are collected to ensure that you fit into our selection criteria for this study and also to provide the necessary information for us to analyze the data collected from you during the experiment.

(1) Gender: _____

(2) Age: _____

(3) Date of birth: _____

(4) Total number of years of education since grade 1: _____

(5) Highest education level (include the current level if you are a student): _____

(6) What did you study (list both major and minor, and any postgraduate courses)?

_____

(7) Any previous neurological diseases? Yes or No

If yes, please provide details: _____

(8) Any previous psychological illness? Yes or No

If yes, please provide details: _____

(9) What is your handedness? Right handed or Left handed or Ambidextrous

(10) Do you wear glasses? Yes or No

If yes, please answer the following:

If you are long-sighted, what is the degree? _____

If you are short-sighted, what is the degree? _____

Other reasons for wearing glasses _____

(11) Is English your first language? Yes or No

(12) Are you a bilingual? Yes or No

If yes, what is your first language? _____

and what is your second language? _____

(13) Do you play music? Yes or No

If yes, how many years have you been playing? _____

Do you have any formal musical training? Yes or No

Please provide details about your formal musical training (i.e., when, how long, and types of musical instrument you played?

_____

(14) Your contact information:

Phone number: _____

Email address: _____

Street address: _____

Part 2 – MRI screening questionnaire

Please fill in the MRI screening questionnaire on the next page. This questionnaire aims to make sure you are safe to undergo MRI scanning for the experiment. Please do not hesitate to let us know if you need more explanation on any of the items. The researcher will go over the questionnaire with you to ensure that you fully understand all the items.

This intake interview was conducted by _____(Investigator or Designee's name)

APPENDIX E PATIENT HISTORY AND MRI SCREENING SHEET

Form E1 Female version

Capital Health
EDMONTON AREA

Patient History and MRI Screening (Female)

CARITAS HEALTH GROUP

Name: _____ Hospital #: _____

The following items may interfere with your Magnetic Resonance Imaging examination, and some can be potentially hazardous.
Please indicate if you have the following:

Section 1

Yes	No	
☐	☐	Cardiac Pacemaker / Automatic Defibrillator
☐	☐	Aneurysm Clip(s)
☐	☐	Implanted Insulin Pump
☐	☐	Implanted Drug Infusion Device
☐	☐	Bone Growth or Bio Stimulator
☐	☐	Neurostimulator
☐	☐	Epicardial Leads
☐	☐	Cochlear Implant
☐	☐	Intra-vascular Coils
☐	☐	Swan-Ganz Catheter

Section 2

Yes	No	
☐	☐	Stents
☐	☐	Any type of surgical clip or staple(s)
☐	☐	Heart Valve Prosthesis
☐	☐	Vena Cava Filter
☐	☐	Middle Ear Implant
☐	☐	Eye Prosthesis
☐	☐	Shrapnel or Bullet
☐	☐	Magnetically operated devices
☐	☐	Wire Sutures
☐	☐	Silver impregnated dressing (Acticoat, Actisorb Plus, Aquacel)

Section 3

Yes	No	
☐	☐	Diaphragm or IUD
☐	☐	Intraventricular Shunt
☐	☐	Intracranial Pressure Monitor
☐	☐	Wire Mesh
☐	☐	Artificial Limb or Joint
☐	☐	Any orthopedic item(s) (i.e. pins, rods, screws, nails, clips, plates, wire, etc.)
☐	☐	Dentures or any type of removable dental item
☐	☐	Hearing Aid
☐	☐	Tattoos
☐	☐	Body Piercings
☐	☐	Transdermal Patches (i.e. nicotine, nitroglycerine, etc.)

Yes	No	
☐	☐	Worked as welder, lathe operator, sheet metal worker or any similar occupation that may result in a metallic foreign object in your eyes.

Have you ever had any surgical procedure or operation? ☐ Yes ☐ No

Type _____ Year _____

Type _____ Year _____

Type _____ Year _____

Have you **EVER** had any metal fragments in your eyes, or had an injury to your eyes with metal? ☐ Yes ☐ No

Do you have a history of kidney failure or are you on kidney dialysis? ☐ Yes ☐ No

Are you pregnant or do you suspect that you are pregnant? ☐ Yes ☐ No LMP _____

Patient Weight _____ lb / kg Patient Height _____ in / cm

I have answered the above questions to the best of my ability.
The MRI examination has been explained to me and I have had my questions answered to my satisfaction.

Signature of Patient or Guardian _____ Date _____

Witness / Technologist _____

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Form E2 Male version

Alberta Health Services

Patient History and MRI Screening (Male)

Covenant Health

Name: _____ Hospital #: _____

The following items may interfere with your Magnetic Resonance Imaging examination, and some can be potentially hazardous.
Please indicate if you have the following:

Section 1

Yes	No	
☐	☐	Cardiac Pacemaker / Automatic Defibrillator
☐	☐	Aneurysm Clip(s)
☐	☐	Implanted Insulin Pump
☐	☐	Implanted Drug Infusion Device
☐	☐	Bone Growth or Bio Stimulator
☐	☐	Neurostimulator
☐	☐	Epicardial Leads
☐	☐	Cochlear Implant
☐	☐	Intra-vascular Coils
☐	☐	Swan-Ganz Catheter

Section 2

Yes	No	
☐	☐	Stents
☐	☐	Any type of surgical clip or staple(s)
☐	☐	Heart Valve Prosthesis
☐	☐	Vena Cava Filter
☐	☐	Middle Ear Implant
☐	☐	Penile Prosthesis
☐	☐	Eye Prosthesis
☐	☐	Shrapnel or Bullet
☐	☐	Magnetically operated devices
☐	☐	Wire Sutures
☐	☐	Silver impregnated dressing (Acticoat, Actisorb Plus, Aquacel)

Section 3

Yes	No	
☐	☐	Intraventricular Shunt
☐	☐	Intracranial Pressure Monitor
☐	☐	Wire Mesh
☐	☐	Artificial Limb or Joint
☐	☐	Any orthopedic item(s) (i.e. pins, rods, screws, nails, clips, plates, wire, etc.)
☐	☐	Dentures or any type of removable dental item
☐	☐	Hearing Aid
☐	☐	Tattoos
☐	☐	Body Piercings
☐	☐	Transdermal Patches (i.e. nicotine, nitroglycerine, etc.)

Yes	No	
☐	☐	Worked as welder, lathe operator, sheet metal worker or any similar occupation that may result in a metallic foreign object in your eyes.

Have you ever had any surgical procedure or operation? ☐ Yes ☐ No

Type _____ Year _____

Type _____ Year _____

Type _____ Year _____

Have you **EVER** had any metal fragments in your eyes, or had an injury to your eyes with metal? ☐ Yes ☐ No

Do you have a history of kidney failure or are you on kidney dialysis? ☐ Yes ☐ No

Patient Weight _____ lb / kg Patient Height _____ in / cm

I have answered the above questions to the best of my ability.
The MRI examination has been explained to me and I have had my questions answered to my satisfaction.

Signature of Patient or Guardian _____ Date _____

Witness / Technologist _____

CH-0186 Aug 2007

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APPENDIX F ADVERTISEMENT

Would you like to participate in a study on "Working Memory Training"?

CALL FOR RESEARCH PARTICIPANTS

If you are a healthy student or young adult aged between 18 and 35 (inclusive), right handed, and have no history of neurological and psychological illness, then this opportunity is right here for you.

We are a research team at the Faculty of Rehabilitation Medicine, University of Alberta (U of A), and looking for volunteers to participate in a working memory training program for four consecutive weeks (twenty days, from Monday to Friday, 1.5 hours a day). The training will be done at home. We will examine your brain activity using functional Magnetic Resonance Imaging (MRI) before and after a course of working memory training. You will perform some cognitive tasks during the MRI scanning. We may also ask you to provide 12 photos of your significant others so that we can assess how your brain processes familiar information in working memory. In addition, we will ask you to come to the Functional and Cognitive Neuroscience Laboratory at the U of A before and after the four-week training and perform some cognitive tasks. This will help us examine how the working memory training will improve your cognitive abilities.

After you completed the study, you will be rewarded a $40 gift card from a local restaurant as a token of appreciation for your participation. If you need transportation to come for the sessions, we will reimburse you ETS tickets. Plus, if you like, we will be happy to give you a computerized copy of your brain image.

There is no known health risk for performing functional MRI and you will be given details about the procedures. We will also do a careful screening to ensure that you are suitable to undergo MRI procedures. The only absolute requirements for the MRI scan are that you do **NOT** have an implanted cardiac pacemaker or any metal implants, pieces of shrapnel, aneurysm clips, or wires in your head.

Your participation is 100% voluntary and you can opt out any time during the study.

So, don't wait and give us a call!!! We will be happy to arrange an intake interview, either by phone or in-person to find out if you are suitable to participate.

If you are interested, please contact:

Dr. Ada Leung, Tel. 780-492-2342
email: ada.leung@ualberta.ca

This research study has been approved by the Research Ethics Board of the University of Alberta.