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The Neural and Cognitive Basis of Cumulative Lifetime Familiarity Assessment

Devin Duke
The University of Western Ontario

Supervisor
Dr. Stefan Köhler
The University of Western Ontario

Abstract

Perirhinal cortex (PrC) has been implicated as a brain region in the medial temporal lobes (MTL) that critically contributes to familiarity-based recognition memory, a process that allows for recognition to occur independently of contextual recollection. Informed by neurophysiological research in non-human primates, fMRI, as well as behavioural work in humans, the current thesis research tests the novel hypothesis that PrC cortex functioning also underlies the ability to assess cumulative lifetime familiarity with object concepts that are characterized by a lifetime of experiences. In Chapter 2, a patient (NB) with a left anterior temporal lobe (ATL) lesion that included PrC as well as an amnesic patient (HC) with a bilateral lesion to the hippocampus were tested on their ability to make lifetime familiarity judgements for object concepts (i.e., concrete nouns). Patient NB made abnormal familiarity ratings for objects concepts relative to matched controls, while patient HC produced ratings that did not differ from control participants. In Chapter 3, I tested healthy young adults on a frequency judgement task and lifetime familiarity task while they underwent fMRI. A region in the left PrC tracked both the perceived frequency of recent laboratory exposure as well as perceived lifetime familiarity. Finally, in Chapter 4, I tested whether indeed lifetime familiarity judgements are based on conceptual processing by making use of an associative priming paradigm. Associatively-related primes increased the perceived familiarity of object concepts while also reducing the latency of these judgements. Overall, the results from all three empirical chapters provides evidence that warrants an extension of PrC functioning to include the cumulative assessment of lifetime familiarity with object concepts.

Keywords

Co-Authorship Statement

The experiments conducted in my thesis were carried out under the supervision of Dr. Stefan Köhler. The study presented in Chapter 2 is currently under review for publication in Neuropsychologia along in collaboration with Dr. Ben Bowles who helped design and analyze the patient data, as well as Dr. Ken McRae and Dr. Shayna Rosenbaum who provided helpful feedback with analyses and writing. The research in Chapter 3 is currently submitted for publication in Cortex, and benefitted from technical insight provided by Dr. Chris Martin. The priming study presented in Chapter 4 was conducted in collaboration with an honours thesis student Anne Sabourin, who provided help with study construction, data collection and analysis. The quality of the research presented in the current thesis benefitted greatly from the insight of fellow Köhler lab member Dr. Edward O'Neil, Dr. Chris Fiaconni, Jordan DeKraker, Anna Blumenthal as well as our newer lab members HY Yang and Jane Kouptsova. This thesis also benefitted from the extensive feedback from my advisor Dr. Stefan Köhler, most importantly.

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List of Abbreviations and Symbols

AI   Autobiographical Interview

ATL   Anterior Temporal Lobe

BOLD   Blood-Oxygen Level Dependent

cm   centimeter

ERC   Entorhinal Cortex

FDR   False Discovery Rate

fMRI   Functional Magnetic Resonance Imaging

FOV   Field of View

FSG   Forward-Cue-To-Target-Strength

iEEG   Intracranial Electroencephalography

IQ   Intelligence Quotient

ISI   Inter-Stimulus Interval

M   Mean

mm   millimeter

MR   Magnetic Resonance

MRI   Magnetic Resonance Imaging

ms   Millisecond

MTL   Medial Temporal Lobe

PhC   Parahippocampal Cortex

PrC   Perirhinal Cortex

ROC   Receiver Operating Characteristic

s   Second

SD   Standard Deviation

SEM   Standard Error of the Mean

T1   Anatomical Magnetic Resonance Image

T2*	Functional Magnetic Resonance Image
TE	Echo Time
TR	Repetition Time
WASI	Wechsler Abbreviated Scale of Intelligence

Chapter 1

1   General Introduction

Recognition memory is the ability to discriminate between stimuli that we have encountered in our past and novel stimuli that we have yet to experience (Mandler, 1980). It is perhaps the most basic form of declarative memory, which allows for the conscious retrieval of information about past experiences and episodes (Eichenbaum, 2000). Recognizing that an object has been previously encountered in our environment is critically important for many aspects of adaptive behaviour. Encoding and recognizing previous experiences with faces and names of conspecifics, landmarks relevant for navigation, or other encounters with living and non-living objects, is necessary to learn from past experience with those stimuli and to adapt to an ever-changing environment. Recognition memory research, to date, has centered most significantly around the assessment of recent incremental changes in memory strength that result from discrete experimental exposures.

There is a consensus in the neuroscience literature across rodents, non-human primates, and humans that recognition memory relies upon the integrity of the medial temporal lobes including perirhinal cortex (PrC) and the hippocampus (Brown & Aggleton, 2001; Eichenbaum et al., 2007; Suzuki & Naya, 2014; for exceptions, see Martin et al., 2013). Recollecting contextual aspects of an experience with a stimulus, such as remembering that you placed your keys on the kitchen counter as opposed to the key hook yesterday, has specifically been associated with hippocampal function. Another more contentious body of research also suggests that the role of PrC in recognition is specific to item-based familiarity assessment (Brown & Aggleton, 2001; Eichenbaum et al., 2007; Montaldi & Mayes, 2010; but see Wixted & Squire, 2011 for other views of PrC). Familiarity assessment is a recognition process that can occur successfully in the absence of retrieving any associated contextual information about a specific past encounter with a stimulus. At the core it provides a feeling that a stimulus is old and it has been suggested to be independent of recollection about the specific time and place of that encounter (Yonelinas, 2002).

From a historical perspective the initial connection made between MTL function and amnesia (i.e., a dense impairment in declarative memory) came from the case study on patient

HM by Brenda Milner and William Scoville in 1957, which spurred the literature on the cognitive neuroscience of human memory (Scoville & Milner, 1957). Patient HM underwent a surgical procedure to treat intractable temporal-lobe epilepsy that involved the resection of hippocampus, PrC and other MTL regions bilaterally. HM demonstrated a complete inability to consciously reflect upon past experiences beginning at the point of his surgery to relieve intractable epilepsy. In the time since this initial investigation occurred, the cognitive neuroscience of memory has progressed dramatically with the advent of fMRI and more precise ways to measure volumetric differences between patients with MTL damage. The study of recognition memory has developed out of the more general study of declarative memory and has connected hippocampal and PrC function as being crucial for recollection and familiarity-based recognition, respectively. Other models of MTL function have avoided making reference to the phenomenology of memory decisions and have chosen to describe the functional roles of PrC and hippocampus as item recognition and contextual retrieval respectively (Davachi et al., 2006; Hannula et al., 2013). Current research on the functional role of the hippocampus has progressed to a more detailed analysis of the differential contribution of hippocampal subfields to pattern completion and pattern separation processes in episodic memory (Yassa & Stark, 2011; Stark et al., 2013).The current thesis will be particularly concerned with the functional role of PrC in different types of familiarity assessment. The role of PrC in familiarity-based recognition has been supported by neuropsychological studies showing that patients with hippocampal lesions have preserved familiarity (Aggleton et al., 2005; Yonelinas, 2002) and by fMRI studies showing that PrC activity is associated specifically with item-based recognition and states of familiarity (Daselaar et al., 2006; Gonsalves et al., 2005; Montaldi et al., 2006; Wang et al., 2014). Additional evidence for this conceptualization of MTL function has also come from more recent studies making use of intracranial recordings in humans, as well as neurophysiological studies with other species.

Familiarity is the process in recognition memory that is the primary focus of the current thesis. Familiarity is most typically explored with recognition memory tasks that require an assessment of recent incremental changes in exposure that result from an experimental presentation of a stimulus. Interestingly, recognition studies often make use of object concepts (i.e., the concrete object that a word or picture refers to; Martin, 2015) that

are tied to a rich cumulative history of past experiences. In other words, object concepts possess a level of absolute familiarity (Mandler, 1980), otherwise known as pre-experimental familiarity that are brought to bear in a recognition memory experiment. For example, for most people, the object concept 'dog' has a higher level of absolute familiarity based on cumulative life experience than 'aardvark'. Furthermore, when people are asked to explicitly reflect upon their lifetime familiarity for various object concepts, their familiarity ratings are strongly correlated with one another (Duke et al., submitted). This suggests that we possess the ability to tap into a cumulative familiarity signal that results from hundreds or thousands of individual experiences across our lifespan. Evidence from a relatively small body of behavioural work also suggests that judgements of recent exposure and pre-existing familiarity levels influence one another, which hints that awareness of cumulative lifetime familiarity and recent incremental changes in familiarity may arise from a common mechanism. To date, very little is known about the brain-basis of lifetime familiarity judgements and whether it relates to the well established role of PrC in recognition memory for stimuli encountered in an experimental study phase.

The thesis research presented here is aimed at determining whether the functional role of the PrC can be extended to include a critical role in the assessment of cumulative lifetime familiarity for object concepts. Towards this end, I will present patient-based neuropsychological research, a functional neuroimaging study in healthy young adults, as well as cognitive experiments aimed not only at determining the role of the PrC in these judgements, but also to uncover to what extent lifetime familiarity judgements rely on conceptual processing. Finally, I will discuss and review how the current thesis research may contribute to existing models of PrC function.

1.1   The Dual-Process Model of Recognition Memory

An enormous amount of research has been devoted to uncovering the processes that contribute to recognizing whether a stimulus has been encountered in the past or is new. Many researchers in the recognition memory literature believe that recognition can be divided into two component processes, recollection and familiarity (Yonelinas, 2002). Recollection is a process that allows for the retrieval of event-specific contextual information. For example,

if you were to recognize a face on the bus and bring to mind the contextual detail that you saw this individual for the first time a week ago at a music festival in town, you would be tapping into recollection. Familiarity on the other hand, is a process that allows for the context-free assessment of prior exposure with a stimulus. A particularly useful example that characterizes the nature of a familiarity-based recognition experiences was put forth by George Mandler in 1980. He presented a hypothetical scenario called the 'butcher-on-the-bus' in which a person has a feeling of familiarity for the town butcher on the public bus without being able to remember who the butcher was or where he was first encountered. The change in context between the butcher's shop and the public bus is thought to leave the person with a mere feeling of oldness (i.e., familiarity) for the butcher due to a lack of contextual overlap between the first and second encounters. This scenario highlights how item familiarity can dissociate from rich contextual recollection in recognition memory.

Recollection and familiarity have typically been measured behaviourally using the study-test paradigm. This involves presenting participants with a controlled list of stimuli to study one at a time, and after a delay participants are required to explicitly discriminate between old stimuli from the study list and novel stimuli presented for the first time at test. When a stimulus has been judged as 'old' by the participant they then make a phenomenological judgement concerning the nature of their recognition experience. This has been coined the 'remember-know' procedure as experiences of recollection are to be accompanied by a 'remember' response and a familiarity-based recognition experience is marked as a 'know' response (Tulving, 1985). Receiver Operating Characteristics (ROC) analyses have also been used commonly to measure these processes through the examination of the shape of the ROC curves (Wais et al., 2006; Yonelinas et al., 1997). It is generally agreed upon that familiarity is a graded or continuous process (i.e., can vary from weak to strong feelings of familiarity) and suggestions have been made that recollection is a threshold process (Yonelinas, 2001).

There is a wealth of evidence in favour of a distinction between familiarity and recollection in the recognition memory literature. Several behavioural manipulations have been found to dissociate with respect to their effects on familiarity-based and recollective responses. It is important to note that some of these manipulations are implemented during

the study phase of the task and others at the time of recognition (i.e., retrieval). Response-deadline procedures have been used to test the differential temporal unfolding of familiarity and recollection (Bowles et al., 2007; Boldini et al., 2004). When a recognition decision at test is to be made as fast as possible within a limited response window, recollection usually suffers while familiarity is left relatively unaffected. This is thought to occur because familiarity is a rapid, item-based, memory signal that is available within the speeded recognition window (within 400ms). The recollection of associative and contextual details unfolds over a longer period of time. Manipulations of processing fluency at retrieval have been found to affect primarily familiarity-based recognition (Rajaram & Geraci, 2000; Duke et al., 2014). In line with the idea that familiarity is a context-free feeling of 'oldness' with a stimulus, these studies have shown that enhancing the conceptual or perceptual fluency of processing for recognition items via priming leads to a misattributed feeling of familiarity for novel test items and also heightened feelings of familiarity for old items.

A great deal of controversy has surrounded the precise neural contributions to familiarity and recollection in the MTL. It is generally agreed upon that PrC critically contributes to familiarity-based recognition, but whether the hippocampus contributes to recollection as well as familiarity has been most greatly debated. Regardless of the specific studies that have or have not provided evidence of a clean dissociation between recollection and familiarity between the hippocampus and PrC, recent studies using intracranial recordings from MTL in humans have provided strong evidence that these two regions are performing largely different functions (Staresina et al., 2013a; Staresina et al., 2013b). Given that the primary emphasis of the current thesis is the role of PrC in the assessment of different types of familiarity assessment, research on the hippocampus will only be mentioned in passing.

1.2   Neuroimaging Studies of PrC Contributions to Item Recognition and Familiarity Assessment

By taking advantage of fMRI and more recently intracranial electroencephalography (iEEG), researchers have reliably identified the PrC as a critically important brain region for item-based or familiarity-based recognition memory. With respect to the MTL more broadly,

researchers have extensively debated the specific contributions of MTL subregions, in particular the hippocampus, PrC, and parahippocampal cortex (PhC) in recognition memory. Blood oxygen level dependent (BOLD) signal fluctuations related to the recollection of contextual aspects of memories have been found in the hippocampus, in-line with its known role in processing spatial context information (see Nadel & Moscovitch, 1997 for review) and relational binding operations (Cohen et al., 1997). In one of many studies in this literature, a comparison of brain activity related to 'Remember' responses in the remember-know paradigm was compared to 'Know' responses, showing a marked increase in bilateral hippocampal activation (Eldridge et al., 2000), while familiarity-based responses in variants of the remember-know procedure was associated with a relative decrease in PrC activity when compared to correctly rejected novel items during test (Gonsalves et al., 2005).

Several studies on recognition memory have reported a negative correlation between confidence in the perceived 'oldness' of items during the test phase and PrC BOLD response (Daselaar et al., 2006; Gonsalves et al., 2005; Montaldi et al., 2006; Wang et al., 2014). Variations in the confidence of "old" judgements during retrieval has been taken as a behavioural indicator of recent changes in item-based memory strength and familiarity (Yonelinas, 2001). In an impressive demonstration by Daselaar et al. (2006), participants took part in a study phase in which a list of words and pronounceable non-words were presented and participants made lexical decisions. After a delay of roughly half an hour, "old" or "new" judgments were required for old and novel test words, and after a judgement was made, participants rated on a 1 to 4 scale how confident they were in their recognition decision. BOLD signal in PrC tracked the confidence feelings of "oldness" in such a way that higher levels of confidence were characterized by the lowest level of PrC activity. This finding is in line with other past studies showing that a PrC familiarity signal manifests as a decrease in BOLD response, akin to a 'repetition suppression' effect (Henson et al., 2003; Montaldi et al., 2006). A study by Montaldi et al. (2006) went a step further and directly asked participants to make familiarity ratings and recollection ratings for stimuli in the test phase and found that PrC activity linearly decreased as feelings of familiarity increased. Hippocampal activity increased for ratings of recollection. While the impression in the literature is that item and familiarity-based recognition is accompanied by a decrease in activity in PrC, other studies have demonstrated that increases in activity, in particular for non-verbal stimuli, can be

associated with familiarity-based recognition experiences (Martin et al., 2015). In fact, a study by Martin et al. (2015) revealed that the behavioural accuracy of recognition decisions in the study-test paradigm can be reliably predicted by activity patterns made up of both relative increases and decreases in BOLD signal in PrC.

Staresina et al. (2012) used iEEG to temporally and spatially dissociate item and source retrieval. Healthy controls underwent fMRI scanning while they took part in a recognition memory task and iEEG was recorded in pre-epileptic patients in both the PrC and hippocampus using the same recognition task. At study, patients and healthy controls were presented with a list of concrete nouns on top of a color block or scene, and during recognition made old or new decisions for words and then made a source judgement concerning which color or scene was presented with it at study. An analysis of the iEEG data revealed several temporally dissociated ERP effects for item recognition and source retrieval. An early PrC effect was found starting roughly 200ms post stimulus onset and a later hippocampal source retrieval effect starting at 400ms, consistent with the purported timing of familiarity and recollection in behavioural studies using response-deadline procedures.

Staresina et al. (2013) convincingly demonstrated that PrC and hippocampus contribute to independent processes in recognition memory by applying state-trace analysis to intracranial electroencephalographic (iEEG) data in humans. In a reanalysis of the iEEG data in Staresina et al. (2012), the authors tested whether there is a unidimensional memory signal present across regions of the MTL, namely the PrC and hippocampus. The recognition paradigm was such that nouns were presented with either a color or a scene source at study in order to be able to parse trials into trials where the noun was only recognized (i.e., item recognition) as well as trials where the item and source was successfully retrieved (i.e., source retrieval). In a unique analysis that has rarely, if ever, been implemented with brain data, it was shown that the state-trace function of iEEG data time-locked to recognition cue words during the retrieval phase was nonmonotonic. This strongly suggests that the nature of EEG fluctuations in PrC and hippocampus have unique functions across different types of recognition memory responses. More specifically, iEEG response in PrC across trials associated with a correct rejection, item recognition and source retrieval did not follow the same pattern as the hippocampus. In-line with past research that has implicated the

hippocampus in context and source retrieval, one primary difference between the functions produced in PrC and hippocampus was that hippocampal activity was maximal for source retrieval (i.e., successful retrieval of color associated with item or a scene image), while activity in PrC did not differ between successful item recognition trials and trials where the source was correctly retrieved. Overall, this study is strong evidence in favor of the idea that the PrC and hippocampus perform distinct mnemonic retrieval processes in the service of recognition memory.

1.3   Neuropsychological Studies of PrC Contributions to Familiarity

Some of the strongest evidence in favor of the idea that PrC critically contributes to item-recognition and familiarity comes from studies of patients with various MTL lesion profiles. These neuropsychological investigations have most notably supported the dissociation between familiarity and recollection by showing that patients with hippocampal damage reliably have recollection deficits while having relatively preserved familiarity-based recognition abilities (Yonelinas et al., 2002; Aggleton et al., 2005; Holdstock et al., 2008; Turriziani et al., 2008; Jäger et al., 2009; Bowles et al., 2010). Patients who suffer hypoxic episodes are commonly tested in recognition memory experiments due to the fact that hippocampal tissue is particularly susceptible to damage, while the surrounding cortex is left preserved (Rempel-Clower et al., 1996). This provides a useful lesion profile to test the contributions of PrC in recognition memory. One such study of patients who suffered ischemic-hypoxic episodes demonstrated that these patients can have a selective deficit in recollective recognition as measured by an ROC method as well as the remember-know procedure (Yonelinas et al., 2002). Importantly, familiarity-based discrimination was relatively normal in this sample of patients. Again taking advantage of the remember-know procedure and ROC analyses, Aggleton et al. (2005) tested patient KN who had significant hippocampal volume reduction (roughly 45%) after having been afflicted by a case of meningitis. KN demonstrated the same pattern of results as the ischemic-hypoxic patients tested by Yonelinas et al. (2002), preserved familiarity but impaired recollection relative to matched controls. Bowles et al. (2010) tested a patient with a left ATL lesion that included the PrC but spared the hippocampus as well as a group of patients with variable levels of

hippocampal pathology resulting from amygdalo-hippocampotomy on a recognition memory task with verbal memoranda. A double dissociation was revealed such that patients with hippocampal damage had relatively preserved familiarity estimates and impaired recollection, while the patient with the left ATL lesion only demonstrated impaired familiarity. These studies provide strong evidence in favour of the idea that the integrity of the PrC is necessary for item-based recognition and familiarity. There have been some cases when estimates of recollection and familiarity were both impaired by hippocampal damage (Manns et al., 2003; Wais et al., 2006). As a result, single-process proponents of MTL function have argued for parsimony when characterizing the neural basis of familiarity and recollection with respect to the HC. Some researchers have settled with a functional characterization of the hippocampus that is not limited to recollection, but may include familiarity (Manns et al., 2003; Wais et al., 2006). It is possible that the inconsistency of hippocampal contributions to familiarity and item-recognition relates is related to the extent of lesion location along the anterior-posterior longitudinal axis of the hippocampus. Regardless of whether the hippocampus contributes to familiarity, it is agreed upon that integrity of PrC function is critical for item recognition.

An important case study was performed by Bowles et al. (2007) that has offered valuable knowledge concerning the role of extra-hippocampal structures in recognition memory. Bowles and colleagues tested patient with a left ATL lesion that included PrC but completely spared hippocampus, a particularly rare lesion profile. Patient NB is a 22 year-old female that developed seizures as a result of a mass growing in her left amygdala. Her surgical resection included left amygdala, roughly 40% of her left PrC, as well as neighboring left lateral and temporopolar regions. One unique aspect of this resection was that the hippocampus was spared in order to minimize the negative effects on episodic recollection. Bowles and colleagues tested patient NB on a battery of study-test recognition tasks to isolate the effects of left PrC damage on familiarity and recollective-based recognition. In three experiments using the remember-know procedure, an ROC approach taking advantage of graded responses of recognition confidence, and a response-deadline procedure, NB demonstrated a selective deficit in familiarity-based recognition. As mentioned previously in Section 1.1, familiarity is thought to be a fast process that signals an immediate, context-free signal of past experience. Following the logic that familiarity is the primary signal used by a participant under speeded retrieval conditions, NB was required to make a fast recognition

decision within 400ms and within a longer period of 2000ms in two different tests. As predicted, NB was significantly impaired relative to controls only in the speeded recognition test. Across three testing methods, this case study provides some of the strongest evidence in favour of a dual process account of recognition at the level of behaviour and MTL localization. An important follow-up study conducted with patient NB by Martin et al. (2011) demonstrated that her familiarity-based recognition impairment was selective to verbal conceptual memoranda and was not present when abstract visual designs were the subject of recognition testing. It was interpreted that her preserved familiarity in relation to recently encoded abstract designs may have been supported by her intact right PrC. Across all of the reviewed research, it is clear that sufficient neuropsychological evidence has accumulated to strongly suggest that item/familiarity signals for recent incremental experimental exposures rely upon the integrity of the PrC in the MTL.

1.4   PrC and Item Recognition in Non-Human Primates

Research in monkey neurophysiology has consistently corroborated the basic contention coming out of the human neuroimaging literature that the PrC plays an important role in item-recognition. I refer to this type of recognition as item-based given that we are not able to confirm the phenomenological state of monkeys while they perform continuous recognition or delayed-match-to-sample tasks as we can with humans using a variant of the remember-know paradigm. Moreover, the tasks used with monkeys only require item-based rather than context-based judgements, making it difficult to determine how neurophysiological findings translate to the familiarity/recollection mapping tested in human research. The literature on the role of PrC in recognition decisions from monkey neurophysiology has benefitted the human recognition memory field given their unique ability to directly record firing rates of neurons in PrC using intracranial electrodes. In a seminal study, Xiang and Brown (1998) noted that PrC neurons differ in their sensitivity to the effects of recent versus cumulative long-term exposure to visual stimuli when monkeys perform recognition memory tasks. Xiang and Brown tested macaque monkeys on a serial recognition task that involved initially training monkeys to discriminate between familiar and novel pictures of objects or scenes and then subsequently recorded from neurons in PrC while they performed the task. Some stimuli were repeated periodically during the session to allow

for a comparison of neuronal firing rate between the first and repeated presentations. They reported that some PrC neurons (termed 'recency neurons') respond to repetition of a recent exposure to a stimulus. Importantly, this response occurred regardless of whether the stimulus was seen by the monkey in many other sessions distributed over multiple days or not (see also Miller et al. 1991; Fahy et al., 1993; Li et al., 1993). Interestingly, Xiang and Brown (1998) found other PrC neurons that responded to whether stimuli had been encountered many times on prior days, regardless of whether they were seen for the first or the second time in the current session ('familiarity neurons'). In addition to 'familiarity' and 'recency' neurons, a third type of neuron was discovered, 'novelty' neurons, which respond only to the first encounter with a stimulus. These findings point to a specific role of PrC in processing different types of item exposure, not just recent discrete exposures.

Across human behavioural, neuropsychological and neuroimaging methods as well as neurophysiological research in monkeys, PrC has been firmly identified as a region in the MTL that subserves item-recognition abilities. While the debate concerning whether PrC integrity is also required for recollection of contextual detail is still underway (e.g. Staresina et al., 2011; Watson et al., 2012), the evidence clearly shows that it is involved in familiarity in numerous task contexts that require reference to recent experimental exposure and that its response profile is different from that of the hippocampus (Staresina et al., 2013). While a consensus has emerged that the PrC is involved in the assessment of recent changes in familiarity for stimuli presented in an experimental study phase, left unanswered is whether the PrC's functional role can be extended to include the evaluation of cumulative levels of lifetime familiarity for object concepts. In order to make predictions concerning the role of PrC in lifetime familiarity judgements, I now review pertinent evidence from (i) cognitive research on the interaction between absolute and incremental familiarity, (ii) other neurophysiological findings in non-human primates, and (iii) human studies focusing on PrC role in conceptual processing and the disambiguation of objects with high feature overlap.

1.5   Pre-Experimental and Lifetime Familiarity

The recognition memory literature has concentrated on the underlying cognitive processes that contribute to a sense of oldness for recent experimentally-controlled

encounters, but oftentimes these studies make use of memoranda that are associated with a lifetime of meaningful experiences. The level of pre-existing or absolute familiarity associated with object concepts used in recognition experiments is typically controlled for by matching old and novel words lists on word frequency, a measure that is correlated with judgements of lifetime familiarity (Cree & McRae, 2003). There are a number of normative databases that have collected concept familiarity judgements from participants for concepts presented as words or pictures (Alario & Ferrand, 1999; Cree & McRae, 2003; Snodgrass & Vanderwart, 1980), and have revealed that lifetime familiarity ratings are remarkably consistent across participants. Presumably, ratings of concept familiarity across different individuals in a given culture are highly correlated with one another due to the fact that most people in that culture (e.g., North America) are exposed to object concepts at similar frequencies and in similar forms of presentation in the real world over the long-term (e.g., printed word, physical encounter with the object, spoken word). The consistency in ratings across people also suggests that humans have the ability to assess cumulative familiarity for an individual object concept. Interestingly, behavioural work in recognition memory has shown that pre-experimental concept familiarity can influence judgements of recent exposure in the study-test paradigm (Balota & Neely, 1980; Glanzer & Adams, 1990; Joordens & Hockley, 2000; Reder et al., 2000; Coane et al., 2011).

The 'mirror effect' in recognition memory has been taken as evidence of a close relationship between the assessment of recent exposure and an object concept's level of absolute familiarity. In the 'mirror effect', it has been shown that high frequency words (e.g., dog or house) are more likely to be confused as having been presented in the study phase of a recognition experiment than low frequency words due to the fact that the object concept itself has a high level of pre-experimental familiarity (Balota & Neely, 1980; Glanzer & Adams, 1990; Joordens & Hockley, 2000; Reder et al., 2000; Coane et al., 2011). More specifically, this influence is characterized by a higher false-alarm rate to novel test items (i.e., calling novel items 'old') that are high frequency words. Additionally, low-frequency words presented in the study phase of the experiment are associated with a relatively higher subsequent hit rate than high-frequency words (i.e., correct "old" judgement at test) because there is thought to be a high level of attentional processing afforded to these stimuli due to their relative rarity. Importantly, using the remember-know procedure, the increase in false-

alarm rates for high-frequency words manifests as an increase in familiarity-based 'know' responses while the increase in hit rate for low-frequency words is characterized by an increase in 'remember' responses (Reder et al., 2000; Joordens & Hockley, 2000; Balota et al., 2002). At a cognitive level people have a difficult time disentangling a recent incremental familiarity signal from a global level of lifetime experience. These findings suggest, perhaps, that feelings of familiarity resulting from a lifetime of experience with object concepts and feelings of familiarity resulting from a discrete study encounter in the laboratory may share a common cognitive or even neural mechanism. Regardless, these results highlight that judgements of recent incremental familiarity are sensitive to an object concept's level of pre-experimental (i.e., baseline) familiarity.

At initial consideration, lifetime familiarity judgments for concepts acquired over a lifetime and those made in recognition-memory experiments may not seem very similar. However, they are similar in that they both require a judgement of subjective memory strength of a currently attended stimulus, and do not require the retrieval of contextual information about a specific encounter to make such a judgement. For example, a person can easily judge that they have a higher level of lifetime experience with the concept 'dog' relative to the concept 'aardvark' without having to bring to mind specific episodes in one's life related to each of those concepts. Both types of memory judgements concern an individual item in memory and require an acontextual assessment of experience with a stimulus. The primary difference between them is that the cumulative lifetime familiarity judgement requires access to an aggregate item signal, perhaps summed over many discrete encounters. While intuitively it seems as if lifetime familiarity assessment can occur without mentally referring to an individual past experience with a concept, at present it is unclear whether contextual information may still be brought to bear in lifetime familiarity judgements. That is, little is known about the cognitive and neural mechanisms that allow humans to make an assessment of lifetime familiarity for object concepts.

1.6   Does PrC Track Cumulative Familiarity with Object Concepts?

One line of evidence that hints at a potential involvement of PrC in signaling cumulative levels of familiarity has come from work in monkey neurophysiology. As previously mentioned, Xiang and Brown (1998) reported neurons in macaque PrC that modulate their firing rate only in relation to whether a visually-presented stimulus was globally familiar to the monkey prior to the recording session (see Fahy et al., 1993 for similar findings). Some stimuli presented during the recording session had been shown to the monkey on previous training sessions, which included many individual presentations. Going one step further toward determining what PrC's role might be in tracking cumulative exposure, Hölscher et al. (2003) found that some PrC neurons track the degree of exposure to objects that accumulates through hundreds of repetitions over the course of weeks. In this study, the response of PrC neurons in the macaque was measured while they performed a serial recognition task similar to that used by Xiang and Brown (1998). One primary difference between Hölscher et al. (2003) and previous studies of non-human primate PrC activity in recognition memory paradigms is that Hölscher et al. recorded from PrC neurons during the build-up of familiarity with the line-drawn objects over many recording sessions. As the monkeys became more familiar with individual objects, the firing rate of a proportion of PrC neurons increased gradually. Importantly, this effect emerged in PrC neurons once stimuli had been presented, on average, 400 times over 1-2 weeks. These studies strongly suggest that some PrC neurons track cumulative experimental exposure to objects, but left unanswered is whether or how human PrC tracks the build-up of familiarity for object concepts associated with a wealth of knowledge and contextual detail. The line-drawings used in the monkey studies is a far cry from the multi-modal object concepts we have repeated personally-significant exposure to over months, years and decades.

Another important consideration is that monkeys were not required to make explicit long-term or cumulative familiarity judgements for the stimuli, but rather, an objective tracking of experience with stimuli was apparent in PrC neuronal responses. It is difficult to know how human PrC may respond when the assessment of lifetime familiarity itself is required based on this evidence. To make an even stronger case that human PrC may play a role in the cumulative assessment of experience with object concepts, it is important next to review research conducted using human neuroimaging that has centered its investigation on the role of human PrC in processing conceptual information in semantic memory.

1.7   Organization of Feature Structure of Object Concepts in PrC

Another source of evidence that PrC plays a role in processing information relevant to concepts acquired through a lifetime of experience comes from work in humans using fMRI. A large number of recent studies have shown that PrC is involved in processing object concepts independently of any explicit requirement to make judgments about a past encounter (O'Kane et al., 2005; Voss et al., 2009; Wang et al., 2010; Dew & Cabeza, 2011; Heusser et al., 2013; Wang et al., 2014). For example, PrC has been shown to influence the generation of associations between concepts, a task that does not require an assessment of recent presentation. In Wang et al. (2014), participants made concrete/abstract judgments for a long list of concepts (e.g., "lemon" or "effect"), and then after a delay, participants were asked to spontaneously generate the first associated word that came to mind in relation to cue words. Some of the cue words were related to concepts presented during the concrete/abstract judgements (e.g., cue word "cause"). Therefore, the production of a word presented during the incidental "encoding" task in the association task would be considered priming. Interestingly, even though there was no requirement by participants to consciously reflect upon the words presented in the abstract/concrete judgement task, PrC activity was related to whether a participant produced a related word from the encoding task. More specifically, PrC activity was reduced during trials in which a related primed word was generated when contrasted with activity during trials in which an associate was produced that was not part of the initial abstract/concrete judgement task.

Some researchers have suggested that conceptual fluency may be the main factor modulating the decreases in BOLD signal seen in fMRI experiments (Dew & Cabeza, 2013; Voss et al., 2009). For example, the tendency for participants to produce conceptually-related words at test may be due to the heightened level of conceptual fluency resulting from the presentation of a related word in the study phase. Interestingly, recognition memory judgements have been found to be sensitive to conceptual priming during the test phase of a study-test recognition experiment, a manipulation that increases the conceptual fluency of test words (Rajaram & Geraci, 2000; Dew & Cabeza, 2013). The tendency to feel as if a target word is old, regardless of test status (i.e., old or new word), increases if a conceptually-related

word precedes the presentation of the target word. In an fMRI experiment by Dew and Cabeza (2013) with a very similar priming design, decreases in PrC activity accompanied targets that were preceded by related prime words. If indeed PrC responds to the conceptual fluency of object concepts, it would be expected that concepts varying with respect to levels of lifetime exposure also vary in their inherent conceptual fluency.

The previously reviewed studies clearly point to a role of PrC in processing recent exposures to object concepts both implicitly and explicitly. In other words, PrC processing is recruited when information concerning a recent encounter is needed, regardless of whether experimental study exposures are explicitly referenced by the participants during cognitive judgements. Another line of studies has convincingly demonstrated PrC involvement in semantic memory tasks that include no recent experimental encounter with concepts (Bruffaerts et al., 2013; Clarke & Tyler, 2014; Liuzzi et al., 2015; Wright et al., 2015). This group of studies has revealed that PrC carries information that is of particular relevance for making fine-grained distinctions among object concepts. More specifically, Bruffaerts et al. (2013) made use of pattern similarity analyses and normative feature data that nicely characterizes the perceptual and other semantic features of concrete concepts. For example, the authors had participants produce as many features concerning object concepts as possible (e.g., cat - has four legs, is a mammal, has fur, functions as a pet). Importantly, based on the feature data provided by participants, the cosine similarity between concepts organized in related categorical clusters could then be calculated (e.g., a bird cluster or an insect cluster). Next, a different group of participants took part in a property verification task for object concepts during fMRI scanning. The authors found that the similarity of brain activity in left PrC reflected the similarity of object concept features produced in the feature generation task. An interesting demonstration of PrC's role in representing the feature overlap of object concepts in semantic memory comes from a recent study of patients with varying degrees of PrC damage (Wright et al., 2015).Wright et al. also made use of feature data for object concepts and found that performance on picture naming and a word-picture matching task was correlated with the degree of PrC damage across a sample of fourteen patients. Patients were impaired at both tasks but only for concepts with a high level of semantic confusability (i.e., concepts with high feature overlap with one another). These results highlight that the

PrC may serve a critical role in the disambiguation of concepts in semantic memory that are highly confusable with other concepts in the world.

Previous research has also implicated PrC in the disambiguation of visual objects characterized by a high level of perceptual feature overlap with other objects (Barense et al., 2007; O'Neil et al., 2009; Lee et al., 2008; Bussey & Saksida, 2007; Erez et al., 2013). Right PrC is particularly engaged by tasks requiring perceptual oddball judgements for two visually-presented objects that are artificial but share a large proportion of individual perceptual features (O'Neil et al., 2009; Lee et al., 2008). It is possible that left PrC codes for the overlap of features in semantic memory that are not necessarily tied to a visually-presented object, while right PrC may play a unique role in disambiguating visually-presented objects that are novel to a participant and are not associated with object concepts characterized by a lifetime of meaningful experiences. Speaking to this laterality-based prediction, a large meta-analysis of almost one hundred fMRI studies of semantic memory conducted by Rice et al. (2015) demonstrated that the left ATL was most commonly recruited in tasks requiring a judgement concerning a written word. Also, past models of ATL involvement in semantic memory tasks point to a particular role of the left ATL in processing verbal content (Gainotti, 2011). Object concepts denoted by a written word that require an assessment of cumulative lifetime familiarity may be processed by left PrC in particular.

Collectively, Bruffaerts et al. (2013), Wright et al. (2015), and other studies investigating the nature of conceptual feature structure processed in human PrC (see also Clarke & Tyler, 2014; Liuzzi et al., 2015), have functionally characterized the human PrC as a region allowing for fine-grained feature distinctions between concrete concepts in semantic memory. This characterization comes from studies in which no explicit recognition memory judgements were required by participants, supporting the notion that PrC may not be a dedicated declarative memory structure, but rather, may be important for both the assessment of recent exposure to concepts as well as the online processing of feature information bound to concepts over a lifetime of exposures. If the PrC subserves the ability to assess recent incremental changes in familiarity resulting from experimental presentations, and it also processes information relevant to a lifetime of experience with the semantic features that

make up those objects in the environment, it is imaginable that PrC is a key structure in the MTL that allows for judgements of lifetime familiarity for object concepts.

1.8   Goals of Current Thesis

The primary aim of my thesis research is to test the idea that human PrC contributes not only to the recent assessment of familiarity resulting from discrete experimental presentation, but also the cumulative assessment of lifetime familiarity for object concepts. To test this novel hypothesis, three main questions were asked:

1.) Does patient NB, a patient with a left ATL lesion that includes PrC but spares the hippocampus, assess the lifetime familiarity of object concepts abnormally?

In Chapter 2, I present a series of behavioural experiments in which I test patient NB on two variants of a lifetime familiarity task. NB has been shown to exhibit selective familiarity impairments in Bowles et al. (2007). In the first experiment, NB and 22 matched controls made lifetime familiarity judgements for object concepts presented as words. Next, NB and 6 matched controls made lifetime familiarity judgements for concepts accompanied by a picture of the object concept itself to determine whether additional visual information would change ratings. Motivated by recent findings in human neuroimaging, I tested whether NB has a particular problem with making lifetime familiarity judgements for concepts that are characterized by a high level of feature overlap with other concepts. I also tested patient HC, an amnesic individual with a bilateral hippocampal lesion, to determine what role, if any, the hippocampus plays in lifetime familiarity judgements. To preview the findings, patient NB produced abnormal familiarity ratings relative to controls using an average correlation method. This abnormality was present even when picture cues were provided to patient NB. Finally, NB produced particularly abnormal familiarity ratings for concepts with high feature overlap with others. Patient HC, on the other hand, made lifetime familiarity judgements that correlated normally with control participants.

2.) Are graded judgements of lifetime familiarity characterized by a graded BOLD signal in left PrC in healthy participants?

In Chapter 3, I aim to gain anatomical specificity of the functional localization of graded lifetime familiarity judgements of object concepts in the brain by testing healthy participants while undergoing fMRI. The nature of NB's lesions was such that not only left PrC damage was present. Some aspects of lateral temporal cortex and temporopolar cortex were also removed as part of the surgical procedure to relieve intractable epilepsy. Thus, to tie left PrC specifically to the assessment of cumulative familiarity, neuroimaging methods with high spatial resolution in healthy participants is needed. In addition, participants made graded judgements of recent experimental exposure (i.e., frequency judgements) to contrast graded signals of recent incremental changes in familiarity as well as cumulative lifetime familiarity. A region in the left anterior collateral sulcus that is part of PrC tracked both the perceived frequency of recent laboratory exposure as well as the perceived lifetime familiarity of object concepts.

3.) Can conceptual priming paradigms uncover whether lifetime familiarity judgements require conceptual processing?

In Chapter 4, I make use of associative priming to characterize the cognitive basis of lifetime familiarity judgements. More specifically, to seek evidence that judgements of lifetime familiarity of object concepts are based on conceptual processing, I presented associatively-related prime words immediately prior to the assessment of cumulative familiarity for a different target object concept. The use of this particular manipulation is motivated by a similar study conducted by Rajaram and Geraci (2000) which found that feelings of recent incremental familiarity were boosted when recognition judgements for words were preceded by an associatively-related prime word. I found that the presentation of a related prime word led to an increase in the perceived lifetime familiarity and also decreased the amount of time participants took to make these judgements relative to unprimed trials.

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Chapter 2

2 Impaired Assessment of Cumulative Lifetime Familiarity for Object Concepts After Left Anterior Temporal-Lobe Resection That Includes Perirhinal Cortex but Spares the Hippocampus

2.1 Introduction

The ability to recognize the prior occurrence of objects in the environment is critical to many aspects of adaptive behavior. There is a consensus in the psychological literature that recognition memory can operate effectively even in the absence of successful recollection of episodic contextual detail about a pertinent past object encounter (Yonelinas, 2002). The process that allows for recognition independent of episodic recollection is often referred to as familiarity assessment.

Familiarity is typically probed in humans with recognition-memory tasks that include an initial experimentally controlled study phase for a list of items. Familiarity-based responses are those in which an item is endorsed as studied, with no reported recovery of contextual detail about that study encounter. Critically, when meaningful stimuli such as words or pictures of common objects are employed, as is the case in the majority of published studies in cognitive neuroscience research on recognition memory (Eichenbaum, Yonelinas, & Ranganath, 2007; Kim, 2013), participants must judge familiarity with reference to the recent experimental encounter rather than with respect to their lifetime of experience, which may have involved tens, hundreds, or thousands of exposures in many different episodic contexts. From this perspective, extant cognitive neuroscience research has primarily probed recent incremental changes in familiarity rather than absolute or cumulative levels (Bridger, Bader, & Mecklinger, 2014; see also Coane, Balota, Dolan, & Jacoby, 2011; Mandler, 1980). Humans can, however, also judge the cumulative familiarity of object concepts (i.e., the concrete object that a word or picture refers to; Martin, 2015) they have encountered over their lifetime as the outcome of many learning episodes. Such judgments show considerable

consistency across participants in normative studies of concept knowledge, and are also known to have some external validity, as reflected in moderate correlations with objective word frequency (Cree & McRae, 2003; Moreno-Martinez, Montoro, & Rodríguez-Rojo, 2014; Schröder, Gemballa, Ruppin, & Wartenburger, 2012). At present, little is known about the cognitive and neural mechanisms that support this ability.

Cumulative familiarity judgments for object concepts acquired over a lifetime and familiarity-based responses in recognition-memory tasks for items from a studied list can be considered similar in that both require an assessment of prior item occurrence without any requirement to recover contextual information about a specific episodic encounter. Perhaps owing to this similarity, it has often been assumed that the recognition-memory paradigm can provide a model to understand lifetime familiarity that hinges on the effects of accumulated semantic knowledge (e.g., Atkinson & Juola, 1974). Whether this assumption is justified, however, is a question that can ultimately only be answered through systematic empirical investigation (see Mandler, 2008, for further discussion).

A well-known and robust empirical finding in cognitive psychology that addresses the relationship between cumulative lifetime and recent incremental changes in familiarity is the mirror effect in recognition memory. It refers to the observation that hit rates are typically higher, and false alarm rates are lower, for low frequency as compared to high-frequency words (Glanzer & Adams, 1990). It has been suggested that high-frequency lures are more often falsely recognized as 'old' because participants mistake familiarity associated with prior lifetime experience as familiarity based on a recent encounter (Greene, 1999; Joordens & Hockley, 2000; Reder et al., 2000). In support of this notion, for example, Reder et al. demonstrated, using the Remember-Know paradigm, differential increases in 'know' responses for high as compared to low frequency lure words. Such findings suggest that, in phenomenological experience, it is not always apparent whether a stimulus feels familiar due to a recent laboratory exposure or due to frequent pre-experimental experience with it in daily life. As such, the effect could also hint at shared neural mechanisms.

There is a consensus in the neuroscience literature across rodents, non-human primates, and humans that recognition memory requires contributions of perirhinal cortex (PrC) in the medial temporal lobe (MTL; Brown & Aggleton, 2001; Murray, Bussey, &

Saksida, 2007; Squire, Wixted, & Clark, 2007; Suzuki & Naya, 2014). There is also considerable evidence to suggest that within the MTL, mechanisms that allow for familiarity assessment are, at least in part, distinct from those that support recovery of contextual detail about a specific recent item encounter (for reviews see Aggleton & Brown, 2006; Diana, Yonelinas, & Ranganath, 2007; Eichenbaum, Yonelinas, & Ranganath, 2007; Montaldi & Mayes, 2010; but see Squire, Wixted, & Clark, 2007). Although it remains contentious how best to characterize the unique functional contributions of different MTL structures, we note that a number of lesion studies have revealed dissociations in patterns of memory impairments that can be captured with the broad distinction between item-based familiarity assessment and episodic recollection (Aggleton et al., 2005; Bowles et al., 2010; Brandt, Gardiner, Vargha-Khadem, Baddeley, & Mishkin, 2009; Horner et al., 2012; Jäger et al., 2009; Mayes, Holdstock, Isaac, Hunkin, & Roberts, 2002; Tsivilis et al., 2008; Turriziani et al., 2008; Vann et al., 2009; Yonelinas et al., 2002; but see Cipolotti et al., 2006; Manns, Hopkins, Reed, Kitchener, & Squire, 2003; Wais, Wixted, Hopkins, & Squire, 2006). Critically, it has been shown that anterior temporal lobe lesions that spare the hippocampus can produce deficits in familiarity assessment that leave recollection intact. We found this pattern of performance in an individual (patient NB) who underwent a rare tailored surgical resection of the left anterior temporal lobe for treatment of intractable temporal-lobe epilepsy that included PrC but spared the hippocampus (Bowles et al., 2007; Cohn et al., 2010; Martin, Bowles, Mirsattari, & Köhler, 2011; see Davidson, Anaki, Saint-Cyr, Chow, & Moscovitch, 2006; for other patients with selective familiarity impairments). Furthermore, we reported that a stereotaxic surgical treatment for temporal-lobe epilepsy that is restricted to the hippocampus and amygdala can produce selective recollection impairments on the same task, and at the same level of overall recognition performance, as the familiarity impairment that was observed in NB (Bowles et al. 2010). This double dissociation provides particularly strong support for the notion that familiarity assessment in the study-test paradigm relies on brain mechanisms that are, at least in part, distinct from those that support recollection. However, these findings to not speak to any potential role of PrC in judgments of cumulative lifetime familiarity.

Recent evidence from functional neuroimaging research suggests that PrC is involved in processing of object concepts even in tasks that do not make explicit reference to any

recent experimental encounter (Dew & Cabeza, 2011; Heusser, Awipi, & Davachi, 2013; O'Kane, Insler, & Wagner, 2005; Voss, Hauner, & Paller, 2009; Wang, Lazzara, Ranganath, Knight, & Yonelinas, 2010; Wang, Ranganath, & Yonelinas, 2014), and even in paradigms that do not include any experimental study phase (Bruffaerts et al., 2013; Clarke & Tyler, 2014; Liuzzi et al., in press). In the latter set of studies, multivariate pattern analyses have revealed that PrC carries information that allows for fine-grained distinctions among similar object concepts. Neuropsychological research in patients with focal temporal-lobe lesions has also demonstrated that the extent of damage to PrC predicts differential behavioural impairments in naming confusable objects with high semantic feature overlap (see Kivisaari, Tyler, Monsch, & Taylor. 2012, for similar evidence in neurodegenerative disease; Wright, Randall, Clarke, & Tyler, 2015). Overall, these findings are part a growing body of research that points to an important role of PrC in disambiguating objects and object concepts with high perceptual or semantic feature overlap in task contexts other than classic recognition-memory tasks (see Clarke & Tyler, 2015; Graham, Barense, & Lee, 2010, for review).

A recent functional neuroimaging study from our lab provides, to our knowledge, the first evidence that implicates left PrC in the assessment of cumulative lifetime familiarity for object concepts. We examined fMRI BOLD responses when participants judged cumulative lifetime familiarity of object concepts or when they judged the degree of recent laboratory exposure to the same type of stimuli. This study implicated left PrC in both types of judgements (Duke et al., submitted). Notably, PrC was the only brain region that tracked perceived levels of recent experimentally-based concept exposure with the typical decrease in BOLD signal that has been reported for old as compared to new items in many prior studies (Daselaar, Fleck, & Cabeza, 2006; Dew & Cabeza et al., 2013; Henson, Cansino, Herron, Robb, & Rugg, 2003) while tracking perceived cumulative lifetime familiarity with an increase in BOLD signal.

In the present neuropsychological study, we aimed to shed further light on the neural mechanisms that support assessment of cumulative lifetime familiarity with object concepts. Specifically, we tested patient NB on variants of the two types of tasks that revealed left PrC involvement in our prior fMRI study (Duke et al., submitted). Given that NB is known to exhibit selective impairments in familiarity-based recognition memory in the study-test

paradigm (Bowles et al., 2007; Bowles et al., 2010; Martin, Bowles, Mirsattari, & Köhler, 2011), we asked whether these impairments extend to frequency judgements and to assessment of cumulative lifetime familiarity. Note that in our past published work on NB, we examined graded familiarity decisions based on the use of a confidence scale for items presented once at study (Bowles et al., 2007; see Yonelinas, 2002, for rationale). Another way to probe graded differences in memory strength is to manipulate the number of item exposures (repetitions) in the experimental study phase, and to administer frequency judgments at test (see Hintzman & Curran, 1994, for rationale). Therefore, we began the current investigation by examining whether NB's familiarity impairments also manifest in abnormal frequency judgments for degree of recent laboratory exposure to names of object concepts (Experiment 1). In Experiment 2 and 3, we then presented the entire set of 541 items included in McRae and colleagues' normative database for object concepts (McRae, Cree, Seidenberg, & McNorgan, 2005), and asked NB to judge the cumulative lifetime familiarity for each item. Given that our task was designed to probe concept rather than word familiarity, we also tested NB under conditions in which visual images of exemplars were provided in addition to concept names as cues (Experiment 3). Finally, in Experiment 4, we sought evidence to establish some specificity with respect to the nature of MTL damage that cause behavioral abnormalities in judging cumulative lifetime familiarity. Here, we tested an amnesic individual (HC) with documented bilateral lesions of the hippocampus and connected subcortical structures, but intact PrC (Olsen et al., 2013; Rosenbaum et al., 2015). HC is known to exhibit deficits in episodic recollection of autobiographical lifetime experiences (Kwan, Carson, Addis, & Rosenbaum, 2010; Rabin, Carson, Gilboa, Stuss, & Rosenbaum, 2012; Rosenbaum et al., 2011). Given that lesions limited to the hippocampus, or the extended hippocampal system, can spare item familiarity with reference to recent laboratory exposure, we asked whether such a lesion could also spare the assessment of cumulative lifetime familiarity of object concepts.

2.2　　Experiment 1 – Frequency Judgements of Recent Laboratory Exposure to Object Concepts in NB

2.2.1   Methods

2.2.1.1   Participants

NB is a right-handed, university-educated woman whose memory deficits and lesion characteristics have previously been documented in detail elsewhere (Bowles et al., 2007; Bowles et al., 2010; Bowles et al., 2011; Martin, Bowles, Mirsattari, & Köhler, 2011). She is a native English speaker who was 26 years old at testing. About 5 years prior to testing, NB underwent a left unilateral lesionectomy as treatment for intractable epilepsy, which was caused by a mass in the left amygdala (for complete case details, see Bowles et al., 2007). Her surgical resection involved the most anterior extent (~1.7 cm) of the lateral and medial temporal cortex in the left hemisphere, and provided full relief from seizures post-surgically. Volumetric analysis of remaining MTL tissue showed that, as compared to the intact right hemisphere structures, the surgery resulted in removal of 83% of the left amygdala as well as 43% of the left perirhinal cortex and 59% of left entorhinal cortex. The left hippocampus and left parahippocampal cortex were spared by the resection. Evidence from an fMRI study also suggests that, despite impoverished inputs from PrC and entorhinal cortex, NB's left hippocampus shows clear signs of functional integrity as reflected in novelty responses that were comparable to those we observed in control participants (Bowles et al. 2011). A post-surgical clinical neuropsychological examination revealed normal cognitive functions in all domains including memory (97th percentile for WMS III Auditory Delayed Index (Recall), except for a low average score (21st percentile) on a test of semantic fluency (see Supplementary Table 1 in Bowles et al., 2007). Our past experimental research has revealed that NB exhibits impairments in familiarity assessment for verbal stimuli with respect to a recent experimental study exposure; these impairments contrast with entirely preserved recollection abilities. Converging evidence in support of this specificity comes from five experiments that employed the remember-know paradigm, receiver operating characteristics of confidence-based recognition decisions, and a response-deadline procedure, respectively (Bowles et al., 2010; Martin, Bowles, Mirsattari, & Köhler, 2011). Notably, NB's familiarity deficits do not manifest as a phenomenological absence of feelings of familiarity but as an impaired discrimination process with reduced accuracy.

Sixteen female, university-educated control participants (Mean age = 23.3, SD = 1.8) also took part in the study. Our research (Experiments 1- 4) was approved by the Health

Sciences Research Ethics Board and the internal Ethics Board of the Department of Psychology at Western University.

2.2.1.2 Materials

The stimuli were 120 concept names from McRae et al.'s (2005) database of object concepts, and 20 non-words (each presented twice) that were matched on number of letters and syllables. The 120 target concepts were divided into six sets of 20 items, which did not differ significantly on length, number of syllables, or any other variable from the normative database. The items in each set were presented 1, 3, 5, 7, 9, or 11 times during the study phase.

2.2.1.3 Procedure

For each trial in the study phase, participants performed a speeded lexical decision task, and were given 1000 ms to respond. The ISI was 500 ms. Participants pressed the "l" button to indicate that the letter string referred to an English word, and "a" if it was a non-word. The word presentations (720 in total) were randomly intermixed with 40 non-words trials (with each of the 20 non-words presented twice). Repeated presentations of the same concept name were separated by at least six trials. Prior to the study phase, participants performed a 10-item practice session to become accustomed to the speeded lexical decision task. Participants were not informed that a frequency judgment task would follow the study phase. After half of the study trials (~15 minutes into the study phase), participants took a break. The test phase began immediately after completion of the study phase. Participants were presented with the 120 concept names one at a time, and were asked to indicate as accurately as possible, using number keys on the keyboard, whether they had seen a given word 1, 3, 5, 7, 9, or 11 times. The test phase was self-paced, and the experiment took about one hour.

2.2.2 Results

To examine the sensitivity of NB's frequency judgments to degree of recent exposure,

we calculated the mean perceived frequency, separately for each study frequency (see Figure 2.1a). We conducted linear regression analyses to assess this relationship, regressing the average perceived frequency values onto the number of presentations for each participant. The regression coefficient reflects the slope of the lines plotted in Figure 2.1b. To assess whether NB's performance was abnormal as compared to controls for this measure, and for those in all subsequent experiments, we used either z-scores or a modified t-test that was specifically developed for experimental single-case studies (Crawford & Howell, 1998). NB exhibited the lowest slope estimate for her frequency judgments, and this estimate was found to be significantly different from the values obtained in control participants (NB, b1 = 0.18; control mean, b1 = 0.43, z = -2.02, $p < .05$; see Figure 2.1b). This pattern of results suggests that NB's previously documented impairments in familiarity-based recognition memory extend to frequency judgements of the degree of recent laboratory exposure to object concepts.
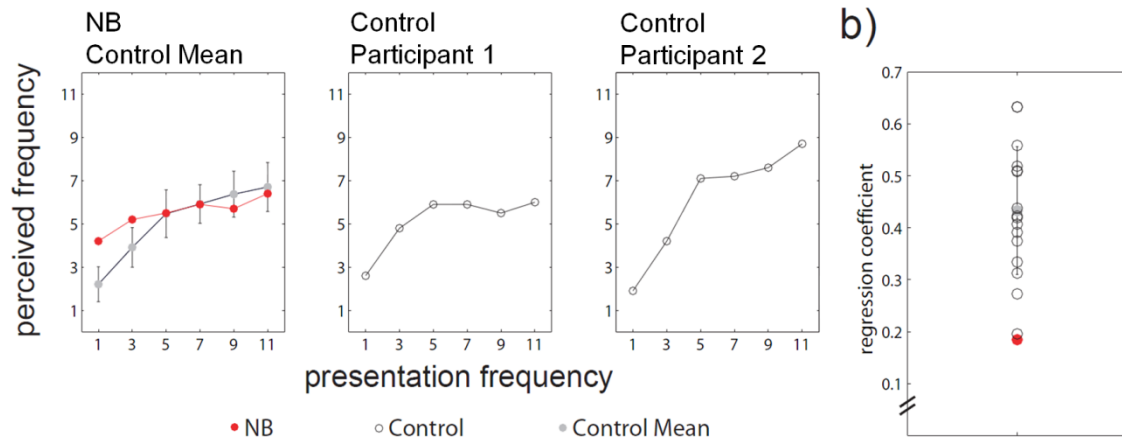
Figure 2.1. Behavioral Results from Experiment 1: (a) perceived frequency as a function of actual presentation frequency for NB , the control mean, and two representative control participants; (b) regression coefficients (slopes) for NB, the control mean, and all control participants. Results reveal impairments in graded judgments of recent frequency of exposure in NB.

2.3 Experiment 2- Lifetime Familiarity Judgements for Object Concepts in Patient NB

2.3.1 Methods

2.3.1.1 Participants

Patient NB and twenty-two healthy female university-educated individuals with English as their first language (Mean age = 24.9, *SD* = 2.8) participated in Experiment 2.

2.3.1.2 Materials

Stimuli were obtained from McRae, Cree, Seidenberg, & McNorgan, 2005). We employed the full set of items in this database, which were from 38 categories of living and nonliving things. Items range from highly familiar (e.g., apple) to relatively unfamiliar (e.g., iguana) in their normative ratings.

2.3.1.3 Procedure

Participants were presented with a verbal label for each of the 541 object concepts in the center of a computer screen one at a time. For each item, they rated long-term prior exposure to the type of object that a word denotes (rather than the word itself). They were required to indicate their answer with a 9-point scale using a computer keyboard in a self-paced manner, with 1 meaning 'not at all familiar' and 9 meaning 'extremely familiar'. It was emphasized that they should choose '9' if the word referred to something they had a great deal of experience with. Participants were encouraged to consider even subtle differences in concept familiarity, and to indicate this in their graded responses.

To determine whether NB's performance was abnormal, we examined item-based correlations (across the 541 concepts) between the ratings NB provided and those of control participants. We computed the mean value of the correlations between NB's ratings and each of the 22 control participants. For purpose of comparison, we also correlated each of the controls' ratings with those of the other controls (as displayed in Figure 2.2a). To analyze the effects of feature overlap on assessment of concept familiarity, we took advantage of a cosine

similarity measure from the normative data base (McRae, Cree, Seidenberg, & McNorgan, 2005) that was computed based on a matrix of 541 concept x 2,526 features obtained in the feature generation task. The cosine between each pair of concepts was calculated based on feature production frequencies. This measure of concept similarity is similar to those used in prior fMRI experiments on object concept representations in PrC (e.g., Bruffaerts et al., 2013). For examination of the effect of feature overlap, concepts were rank-ordered based on this measure; the 100 concepts with the highest score (i.e., highest feature overlap) were chosen and compared with the 100 concepts with the lowest scores in the distribution. We then computed item-based correlations across each set of 100 concepts between the ratings NB provided and those of control participants, following the same approach as employed in our main analyses. Table 2.1 provides data on the category composition of these two subsets of items. As in prior related studies (e.g., Wright, Randall, Clarke, & Tyler, 2015), items with high feature overlap primarily belonged to categories of living things.
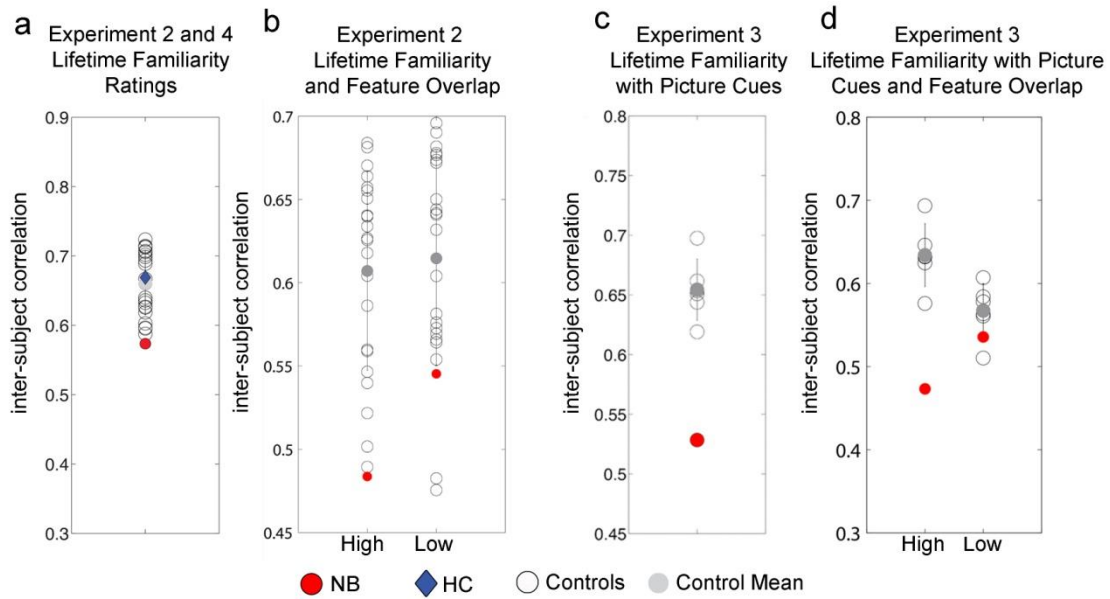
Figure 2.2. Behavioral Results in Experiments 2 – 4. (a) Mean correlation of NB's (Experiment 2) and HC's (Experiment 4) lifetime familiarity ratings with those of 22 control participants and mean correlations between individual controls. (b) Correlations for NB and controls separated for items with high and low feature overlap in Experiment 2. (c) Mean correlation of familiarity ratings for NB and 6 controls in Experiment 3 in which photographs of concepts were added as cues. (d) Correlations for NB and controls separated for items with high and low feature overlap in Experiment 3. Error bars reflect SEM. Correlations reveal abnormal lifetime familiarity ratings in NB. NB has abnormal ratings only for concepts with high feature overlap. There was no evidence for abnormalities in patient HC.

High Overlap	Animals	Fruits/Veggies	Non-living	Other
	43.9%	12.3%	43.9%	0%
Low Overlap	Animals	Fruits/Veggies	Non-living	Other
	0%	0%	89.5%	10.5%

Table 2.1. Percentage of object concepts from different semantic categories in the item sets with High or Low feature overlap item sets as analyzed in Experiment 2 and 3.

2.3.2   Results

When we examined item-based correlations (across the 541 object concepts) between the ratings NB provided and those of control participants, we found that NB's correlation value was the lowest and differed significantly from control participants ($t(21)$ = -1.87, $p <$ .05; see Figure 2.2a). Thus, her ratings are abnormal by virtue of not following the pattern of relative differences in familiarity observed in controls across the large set of tested concepts. Additional analyses also suggested that these abnormalities in rated concept familiarity were present against a background of otherwise normal task performance. Specifically, NB's lifetime familiarity ratings were in the normal range in terms of rating latency (control mean = 2751 ms; NB = 2843 ms; z = 0.04, $p >$ .9), mean rating (control Mean = 4.98; NB = 4.60; z = -0.36, $p >$ .7), and the standard deviation of the ratings (control Mean = 2.54; NB = 2.98; z = 1.31, $p >$ .7). NB's distribution of responses across the nine options also did not appear to differ from that of control participants (see Figure 2.3). To investigate this issue statistically, we used Chi-square tests that compared the distribution for NB, and each individual control participant, to the mean response distribution for all control participants. We found that NB's response distribution did not differ from the control mean any more than that of the 22 control participants (control Mean χ^2= 84.52; NB χ^2= 24.22; z = -1.20; $p >$ .2; see Figure 2.3).

Returning to NB's abnormalities in judged lifetime familiarity, we also examined NB's ratings separately for concepts that show a high versus a low degree of similarity to other concepts in the set of 541 items (as indexed by a cosine similarity measure from the normative data base; McRae, Cree, Seidenberg, & McNorgan, 2005). The correlation value for NB's ratings differed from those of controls for object concepts that had a high degree of semantic similarity ($t(21)$ = -2.12, $p <$ .05; Figure 2.2b) but not for object concepts that had a low degree of similarity ($t(21)$ = -0.98, $p >$ .3) with the other items in the set. This pattern of abnormalities across item sets also held when object concepts that had a high versus a low degree of semantic similarity were matched in terms of normative concept familiarity ($t(21)$ = 2.22, $p <$ .05; $t(21)$ = -1.42, p = .17). As such the specificity of these abnormalities in NB do not reflect difficulties in judging concept familiarity in a particular range of familiarity values, but rather appear to relate to requirements to make fine-grained concept distinctions.
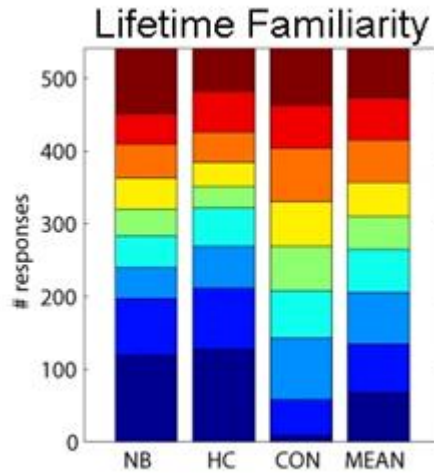
Figure 2.3. Response distributions for patient NB, HC, a representative control participant and the control Mean in Experiment 2 (NB) and 4(HC). Different colors indicate different response options on the 1-9 scale for familiarity ratings. For lifetime familiarity judgments, we found that NB's response distribution did not differ from the control mean (MEAN) any more than that of the 22 control participants (control Mean $\chi^2 = 84.52$; NB $\chi^2 = 24.22$; $z = -1.20, p > .2$). Patient HC did not show any evidence of abnormal lifetime familiarity assessment.

2.4   Experiment 3 – Lifetime Familiarity Judgements in NB with Picture Cues

2.4.1 Methods

2.4.1.1 Participants

NB and six female university-educated controls (Mean age = 26.8, *SD* = 6.6) participated in Experiment 3.

2.4.1.2 Materials

Stimuli were the same concept names as used in Experiments 2, complemented by 541 photographs of corresponding exemplars. Pilot experiments were conducted to ensure that images consistently elicited the targeted concept names in healthy participants. Effects of feature overlap were examined based on the same two subsets of items as employed in Experiment 2.

2.4.1.3 Procedure

The procedure for judgments of long-term exposure to these object concepts was identical to Experiment 2 with the exception that, prior to the presentation of each concept name, the photograph of the corresponding object was shown for 3s and participants were asked to name it. Trials were separated by a 750 ms ISI.

2.4.2 Results

Given that our task was designed to probe concept rather than word familiarity, we aimed to determine in Experiment 3 whether NB's ratings would stay abnormal even when visual images were provided as additional cues with a requirement to name the object shown. When we examined participants' naming accuracy, NB's performance across the 541 photographs was in the normal range (NB: 73.8%, control Mean = 77.4%, range = 66.4 - 79.1%, z = 0.77, *p* > .4). Notably, this pattern held regardless of whether object concepts had high or low feature overlap with the other items in the set examined (NB (high overlap)=

78.9%, control Mean = 71.3%, range = 59.6 - 80.7%; NB (low overlap)= 84.2%, control Mean = 77.5%, range = 77.2 - 82.5%). Contrasting with her naming performance, NB's familiarity ratings were found to be abnormal (see Figure 2.2c; $t(5) = -4.54$, $p < .003$). Furthermore, as in Experiment 2, these abnormalities were again noticeable only for object concepts that had high feature overlap with other items in the set (high feature overlap: $t(5) = -3.94$, $p < .006$; low feature overlap: $t(5) = -0.90$, $p > .4$; see Figure 2.2d). These results offer a replication of our main finding in Experiment 2, and suggests that her abnormalities in judging cumulative lifetime familiarity do indeed extend beyond the processing of verbal cues.

2.5 Experiment 4 – Lifetime Familiarity Judgements in Patient HC

2.5.1 Methods

2.5.1.1 Participants

HC is a well-documented developmental amnesic patient who has participated in several previous studies (Adlam, Vargha-Khadem, Mishkin, & De Haan, 2005; Kwan, Carson, Addis, & Rosenbaum, 2010; Hurley, Maguire, & Varha-Khadem, 2011; Olsen et al., 2013; Rabin, Carson, Gilboa, Stuss, & Rosenbaum, 2012; Rosenbaum et al., 2011; Vargha-Khadem et al., 2003). She is a right-handed female who was 22 years old at the time of testing, with a total of 14 years of education. HC suffered hypoxia perinatally as a result of premature birth. MR-based volumetric analyses have revealed a selective hippocampal lesion with significantly reduced volume in anterior sections bilaterally and additional volume reductions in the right posterior hippocampus (Olsen et al., 2013). Critically, perirhinal (PRC), entorhinal (ERC), and parahippocampal cortices appear to be fully preserved and show no volume reduction. Additionally, it has been found that HC has abnormal morphology of the fornix and absent mammillary bodies, suggesting that a prenatal etiology, rather than perinatal hypoxia, may account for her amnesia (Rosenbaum et al., 2014).

HC exhibits clear signs of amnesia with pronounced impairments on clinical neuropsychological tests of long-term memory, in experimental tasks of recognition memory, and in tasks of autobiographical memory. To illustrate, on the California Verbal Learning Test, HC's impaired performance is reflected in a *z*-score of -4 for short delay free recall, -3 for long-delay free recall, and -2 for long-delay recognition memory. Her WASI Full Scale IQ is in the 66th percentile, and semantic fluency (animals) is above the 90th percentile (see Rosenbaum et al., 2011, for full neuropsychological profile). Testing of autobiographical memory with the Autobiographical Interview (AI) and the Galton–Crovitz paradigms has revealed that HC's autobiographical recollections lack episodic detail across her life-span (see Kwan, Carson, Addis, & Rosenbaum, 2010, Rosenbaum et al., 2011, Rabin, Carson, Gilboa, Stuss, & Rosenbaum, 2012). Ten healthy control participants (Mean age = 22.1, *SD*= 1.9; 9 females) also took part in Experiment 4. They were closely matched with HC in educational background (duration *M* = 14.2 years, *SD*= .93). Research on HC was part of a larger program (directed by S. Rosenbaum) that was approved by the Research Ethics Boards of York University and Baycrest Centre in Toronto and Fanshawe College in London, Ontario.

2.5.1.2   Materials and Procedures

Materials and Procedures were identical to those in Experiments 2.

2.5.2   Results

We first compared HC to the sample of individuals who had served as control participants for NB in Experiment 2. HC's performance was normal on every measure examined, including the mean correlation between her ratings and those of the controls (*t*(21) = 0.16, *p* > .8; see Figure 2.2a). We also tested a second sample of 10 control participants who were matched more closely to HC in terms of educational background. Critically, the correlation between HC's concept familiarity ratings and those of controls again did not differ (*t*(9) = 1.03, *p* > .3). Moreover, when we split the item set into subgroups of object concepts with high or low feature overlap (as reported for Experiment 2 and 3), we did not observe any abnormalities in this comparison for either set (*p* > .05). Overall, these data suggest that judging the familiarity of concepts based on lifetime experience does not depend on the

integrity of the hippocampus and can be preserved even when impairments in autobiographical recollection of specific lifetime episodes are clearly present.

2.5.3 General Discussion

In the present study, we conducted three experiments with an individual (NB) who had previously been found to exhibit selective impairments in familiarity assessment on verbal recognition-memory tasks based on a recent experimental study exposure. Here we asked whether NB might also exhibit impairments in assessing cumulative prior experience with object concepts. As NB exhibits entirely normal recollection abilities, her case presents a unique opportunity to examine links between familiarity impairments in study-test paradigms and possible impairments in familiarity judgments tied to life experience more generally. In the first experiment, we demonstrated that NB's impairment in making recognition judgments extends to cumulative frequency judgments for exposure to concept names in a recent study episode. Experiments 2 and 3 revealed that NB's impairments do indeed extend to abnormalities in judgments of cumulative lifetime familiarity for object concepts. These abnormalities were not limited to verbal processing, and were present even when pictures were offered as additional cues. Moreover, they had some behavioral specificity; we observed them only for judgments on object concepts with high feature overlap in both experiments. Finally, in Experiment 4, we found that an amnesic patient (HC) with previously established deficits in autobiographical memory, due to a well-documented lesion of the extended hippocampal system, does not exhibit any abnormalities in assessing cumulative lifetime familiarity.

Taken together, the pattern of behavioural results from NB and HC strongly suggest that contributions of extra-hippocampal temporal-lobe structures are essential for the assessment of cumulative lifetime familiarity for object concepts. That NB's anterior temporal lesion included left PrC is of particular relevance given that PrC has previously been shown to play a role in familiarity-based recognition-memory for a recent experimental item exposure, as well as in conceptual processing across a variety of semantic tasks (fMRI and lesion mapping; Clarke & Tyler, 2015). While, based on the current findings, we cannot conclusively assert that the behavioural abnormalities we observed in NB are specifically tied

to the inclusion of left PrC in her lesion, we note that fMRI data in healthy young adults from our laboratory have implicated left PrC in performance on the two tasks employed here (Duke et al., submitted; i.e., Chapter 3). In that study, part of left PrC tracked the perceived frequency of recent experimental exposure with a decrease in signal, and the perceived cumulative lifetime familiarity of object concepts with an increase in signal. Notably, we found no other region in left anterior lateral or temporopolar cortex (i.e., in structures that were also affected by NB's resection) that tracked perceived lifetime familiarity in that study. Moreover, the specific part of left PrC that showed this response profile in healthy individuals corresponded to tissue resected in NB, as confirmed on post-operative structural MRI scans.

The notion that PrC carries signals about cumulative prior item exposure over extended time periods is consistent with findings obtained with neurophysiological recordings in non-human primates. In this work, it has been shown that some PrC neurons track the degree of exposure to objects that accumulates through hundreds of repetitions over the course of weeks (Hölscher, Rolls, & Xiang, 2003; see Peissig, Singer, Kawasaki, & Sheinberg, 2007, for related findings from event-related scalp potentials). There is also evidence to suggest that PrC neurons differ in their sensitivity to effects of recent versus long term exposure when monkeys perform recognition memory tasks. For example, Xiang & Brown (1998) reported that some PrC neurons (termed 'recency neurons') respond to repetition of a recent (i.e., within-session) stimulus encounter while other responded to whether stimuli had been encountered frequently on prior days ('familiarity neurons'). It is noteworthy that in prior neurophysiological research, long-term familiarity signals in PrC were observed in the absence of any behavioral requirement to judge cumulative exposure across multiple sessions (Fahy, Riches, & Brown, 1993; Hölscher, Rolls, & Xiang, 2003; Xiang & Brown, 1998). In the current study, by contrast, we observed abnormalities in NB's performance while she was required to make explicit judgements about cumulative lifetime exposure to object concepts. Taken together with our previously mentioned fMRI findings, this evidence suggests that PrC computations have direct behavioral relevance for the assessment of lifetime concept exposure.

The current findings are of special relevance to a growing body of evidence that links human PrC to processing of object concepts in task contexts other than classic

recognition-memory paradigms. In several conceptual priming studies, repeated exposure to object concepts, sometimes across stimulus formats or modalities, led to changes in fMRI signal in PrC that were associated with benefits in behavioral performance on tasks that made no reference to any prior experimental exposure (Dew & Cabeza, 2011; Heusser, Awipi, & Davachi, 2013; O'Kane, Insler, & Wagner, 2005; Voss, Hauner, & Paller, 2009; Wang, Lazzara, Ranganath, Knight, & Yonelinas, 2010; Wang, Ranganath, & Yonelinas, 2014). Past fMRI research has also implicated human PrC in conceptual processing in tasks that did not involve any experimental manipulation of stimulus repetition, including tasks that required naming of visually presented objects or judging the presence of specific semantic features in object concepts denoted by words (Bruffaerts et al., 2014; Clarke & Tyler, 2014; Liuzzi et al, 2015). These studies relied on multi-voxel pattern analyses techniques and have shown that the semantic similarity of object concepts, as reflected in the degree of semantic feature overlap calculated based on feature norms, is reflected in the similarity of fMRI response patterns in left PrC. Such evidence has been interpreted as support for theoretical models of PrC functioning that emphasize its critical role in differentiating between visually (Cowell, Bussey, & Saksida, 2010; Graham, Barense, & Lee, 2010; Murray & Bussey, 1999) and semantically similar objects (Clarke & Tyler, 2015; Taylor, Devereux, & Tyler, 2011). Most pertinent for the interpretation of the current findings, it has been proposed that PrC supports computations that are necessary for establishing fine-grained representations of object concepts that allow for the resolution of semantic confusability (Clarke & Tyler, 2015). Although abnormalities could be revealed in the present study when NB's performance measures were calculated across the entire set of 541 items, follow-up analyses showed that they were driven by abnormal ratings for confusable concepts with high feature overlap (as reflected in the cosine-similarity value in the semantic feature norms; Cree & McRae, 2003; McRae, Cree, Seidenberg, & McNorgan, 2005); NB's judgements for object concepts with limited feature overlap tended to be in the normal range. Differential impairments in discriminating between concepts with high semantic feature overlap have previously been reported in the context of object naming. In two group studies, lesion overlap analyses addressing the extent of damage in the anterior temporal lobe allowed the authors to attribute these impairments specifically to

damage in PrC (Kivisaari, Tyler, Monsch, & Taylor, 2012; Wright, Randall, Clarke, & Tyler, 2015). To our knowledge, the present findings in NB are the first to reveal differential abnormalities in processing confusable object concepts in the context of judgments of cumulative lifetime familiarity.

Although the structure of the task we employed to probe lifetime familiarity did not require any reference to a specific past episodic encounter, it is interesting to consider whether episodic recollection may have still played a role in performance. This possibility deserves consideration in light of prior evidence that implicates hippocampal functioning in ostensibly semantic tasks, such as object naming or conceptual fluency, i.e., the speeded generation of exemplars from different semantic categories (Klooster & Duff, 2015; Greenberg, Keane, Ryan, & Verfaille, 2009; Ryan, Cox, Hayes, & Nadel, 2008; Sheldon & Moscovitch, 2013; Westmacott & Moscovitch, 2003; Whatmough & Chertkow, 2007). Building on the widely held view that the hippocampus plays a critical role in binding items to episodic contexts (Cohen & Eichenbaum, 1993), such evidence has led to the suggestion that episodic and semantic memory may interact even on tasks that do not require any recollection, and that recollection of a pertinent autobiographical episode can help generate or retrieve semantic information (see Sheldon & Moscovitch, 2012, for detailed discussion). To explore this issue in the context of the current task, we conducted a supplementary behavioural experiment in a separate group of healthy young participants (n= 31), in which we asked participants to judge not only lifetime familiarity but also the perceived ease of recovery of a relevant autobiographical episode for object concepts taken from the normative dataset (McRae, Cree, Seidenberg, & McNorgan, 2005). Both types of ratings were obtained in separate blocks of the experiment. Indeed, the resulting data revealed a moderate correlation ($r = .49$) across items; averaged across participants $p < .05$) between perceived lifetime familiarity and perceived ease of autobiographical recollection of a pertinent past episodic encounter. Although these results are in line with a possible contribution, the current data in patient HC argue against any necessary role for autobiographical recollection in assessing lifetime familiarity. Even though HC has autobiographical recollection impairments that have been documented in several previous studies, including in response to the names of object concepts in the Galton-Crovitz task (Kwan, Carson, Addis, & Rosenbaum, 2010; Rosenbaum et al., 2011), her ratings for lifetime familiarity of object concepts did not differ

from the pattern we observed in two different samples of healthy control participants. This pattern of results suggest a functional distinction between the recollection of the time and place of particular autobiographical instances of object encounters, and the assessment of degrees of experience over hundreds or thousands of encounters across different episodic contexts.

In conclusion, the neuropsychological findings reported in the current study provide support for a functional link to be made between the assessment of recent changes in familiarity of object concepts, as probed with experimental study-test paradigms, and cumulative lifetime familiarity based on autobiographical experience accrued outside the laboratory. Moreover, they argue in favor of the notion that recognition of prior occurrence of objects is closely related to the representation of feature-based concept knowledge, likely through computations in PrC. As such they also offer a new bridge between the typically distinct cognitive neuroscience literatures on recognition memory and semantic knowledge representation.

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Chapter 3

3 Role of Left Perirhinal Cortex in Assessing the Cumulative Lifetime Familiarity of Object Concepts

3.1 Introduction

The ability to recognize prior occurrences of objects in the environment is critical to many aspects of adaptive behavior. There is a consensus in the neuroscience literature across rodents, non-human primates, and humans that it requires the integrity of perirhinal cortex (PrC) in the medial temporal lobe (Brown & Aggleton, 2001; Eichenbaum et al., 2007; Suzuki & Naya, 2014; for exceptions, see Martin et al., 2013). A noticeable but less consistent body of research also suggests that the role of PrC in recognition is specific to item-based familiarity assessment (Brown & Aggleton, 2001; Eichenbaum et al., 2007; Montaldi & Mayes, 2010; Ranganath & Ritchey, 2012; but see Wixted & Squire, 2011).

Familiarity is typically probed in humans with recognition-memory tasks that rely on an initial experimentally controlled study phase for a list of items. Responses are classified as familiarity-based when an item is endorsed as studied, with no evidence of successful recovery of contextual detail about that study encounter. Critically, when meaningful stimuli such as object concepts (i.e., the concrete object that a word or picture refers to; Martin, 2015) are employed, as is the case in the majority of published studies (Kim, 2013), participants make their memory judgment with reference to the recent study episode rather than with respect to their lifetime of experience, which may have involved hundreds or thousands of item encounters in many different episodic contexts. As such, extant research on the role of human PrC in recognition memory for meaningful stimuli has typically examined recent incremental changes rather than absolute levels of familiarity (Mandler, 1980; see Mandler, 2008; for further discussion see Bridger, Bader & Mecklinger, 2014).

Behavioral findings suggest that humans can also judge the cumulative experience with object concepts they have had across many different episodic contexts, and over extended time periods. For example, people can easily judge whether they are more familiar with pliers

or scalpels. Indeed, in normative databases on conceptual knowledge (Cree & McRae, 2003; Moreno-Martinez, Montoro & Rodriguez-Rojo, 2014; Schröder, Gemballa, Ruppin & Wartenburger, 2012), participants are often asked to rate their cumulative familiarity with object concepts over their lifetime (sometimes simply referred to as 'concept familiarity'). Such judgments display considerable consistency across participants, and are also known to have some external validity, as reflected in significant correlations with objective word frequency (Cree & McRae, 2003; Moreno-Martinez, Montoro & Rodriguez-Rojo, 2014; Schröder, Gemballa, Ruppin & Wartenburger, 2012). The neural mechanisms that support this ability, however, are poorly understood at present. In particular, it is unknown whether judgments of cumulative lifetime familiarity of object concepts also rely on PrC functioning.

Two sources of evidence hint at a potential role of PrC in signaling cumulative levels of prior object exposure over the long-term. First, neurophysiological recordings in non-human primates have shown that some PrC neurons track the degree of exposure to objects that accumulates through hundreds of presentations over the course of weeks (Hölscher, Rolls & Xiang, 2003; Rolls, Franco & Stringer, 2005). Their cumulative increase in responding contrasts with the decrease that is typically observed in relation to repetition within experimental sessions, a phenomenon that has been coined repetition suppression (Fahy, Riches & Brown, 1993; Li, Miller & Desimone, 1993; Miller, Li & Desimone, 1991; Xiang & Brown, 1998). A second source of evidence comes from a neuropsychological case study from our laboratory, which recently showed that an individual (NB) with a rare left anterior temporal lobe lesion that includes PrC but spares the hippocampus exhibits impairment in judging cumulative lifetime familiarity for object concepts (Chapter 2). This individual was also impaired in making frequency judgments for graded exposure to concept names in a recent experimental study phase, and in making familiarity-based memory judgments in other experimental paradigms that required reference to a study phase (Bowles et al., 2007; Martin et al., 2011). Our findings in NB suggest that left anterior temporal structures play a necessary role in assessing cumulative lifetime experience with object concepts. However, NB's lesion, which resulted from surgical resection, was not restricted to PrC and included anterior-lateral and temporo-polar cortex as well. Thus, these neuropsychological findings do not precisely point to PrC. Given that neighboring anterior temporal structures in the left hemisphere have also been implicated in conceptual processing (e.g., Jackson, Hoffman, Pobric & Lambon-

Ralph, 2016; Skipper, Ross & Olsen, 2011; Wright, Randall, Clarke & Tyler, 2015), it is important to seek evidence that allows for a more precise localization.

In the present study, we employed functional magnetic resonance imaging (fMRI) in healthy individuals to examine whether the role of human PrC in recognition of prior occurrence does indeed extend to the assessment of cumulative lifetime familiarity of object concepts accrued outside the laboratory. For purpose of comparison, we also included frequency judgments that required assessment of degree of recent item exposure in an experimental study phase. We provide evidence that left PrC tracks the perceived degree of prior exposure to object concepts in both types of recognition judgements.

3.2   Materials and Methods

3.2.1   Participants

Twenty healthy young adults (mean age = 25.6, SD = 3.9, 10 females) participated in the experiment. Participants were pre-screened to rule out the presence of neurological disorders. This research was approved by the Health Sciences Research Ethics Board at Western University.

3.2.2   Materials

Two hundred verbal labels for basic-level object concepts were drawn from the normative database on object concepts published by McRae et al. (2005)(see also Cree & McRae, 2003). Two sets of 100 words were used, and were matched on word frequency, word length, number of syllables, and the range and mean of normative concept familiarity ratings (i.e., normative ratings of lifetime concept exposure; Cree & McRae, 2003). Assignment of sets to tasks was counterbalanced across participants. Creation of subsets of items with different familiarity values was based on normative ratings; we selected five subsets of 20 items with progressively increasing levels of normative lifetime familiarity, with items in each set matched on word length and number of phonemes. For frequency judgments of recent exposure, 5 subsets of 20 object concepts, matched for mean normative lifetime familiarity, were assigned to one of the five repetition conditions during the initial study phase. For the lexical-decision task at study, forty pronounceable non-words were also

employed as fillers. Presentation order at study was constrained such that any stimulus repetition was separated by at least 3 trials.

3.2.3   Procedure

During an initial study phase, participants were exposed to the set of 100 object concepts later to be probed in the frequency-judgment task, in combination with the non-word filler items (see Figure 3.1). Each item was presented for 1000ms with a 500ms inter-stimulus interval (ISI). Participants made lexical-decision judgments and were asked to respond as quickly as possible. They were also informed that some stimuli would be repeated. The five subsets of object concepts were presented 1, 2, 4, 7, or 12 times, respectively. The subsequent test phase provided the fMRI data of interest and included 5 runs with 40 experimental trials per run. Here, participants made frequency judgments for the object concepts presented in the recent study phase or judgments of cumulative lifetime exposure for the other set of 100 object concepts (not presented at study). For the latter task, participants were asked to rate their lifetime familiarity with the type of 'thing' (i.e., object concept) the word denotes. For the frequency task, participants judged relative repetition frequency from the initial study phase for each concept. Both types of judgements required use of a 5-point scale, with 1 corresponding to the lowest value (Figure 3.1). Items were presented in five-trial blocks of each task for 2500ms (per item), with a jittered ISI that ranged from 2,500ms to 10,000ms, and the order of trials and jitter optimized within each fMRI run, using the OptSeq2 algorithm (http://surfer.nmr.mgh.harvard.edu/optseq/).
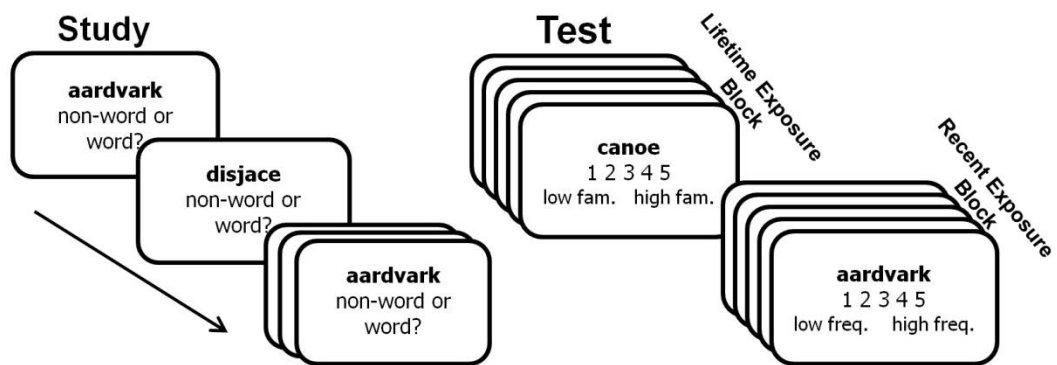
Figure 3.1. Procedure and trial structure. Data from the test phase provided fMRI data of interest.

3.2.4   Functional Data Acquisition and Analysis

fMRI data were obtained on a 3T Siemens TIM Trio scanner using a T2*-weighted single-shot gradient echo-planar acquisition sequence (repetition time (TR) 2500ms; echo time (TE) 25ms; slice thickness 3mm; in-plane resolution 3 x 3 mm; field of view (FOV) 192 x 192 mm; flip angle, 70˚. To optimize MR signal in the most inferior and anterior aspects of the temporal lobe, we used an oblique transverse slice orientation. Each of the 171 functional volumes included 42 contiguous slices collected in an interleaved manner that covered the entire brain volume except for the most superior aspects (< 10 mm) of frontal and parietal cortex. T1-weighted anatomical images were obtained using an MPRAGE sequence (192 slices; TR 2300ms; TE 4.25ms; flip angle 9º; FOV 256 x 256 mm; 1mm isotropic voxels). Data were preprocessed using BrainVoyager QX version 2.6 (Brain Innovation). Functional images were slice-scan time corrected, motion corrected, and high-pass filtered. Functional images were subsequently co-registered with the anatomical images in Talairach space, and smoothed using a three-dimensional Gaussian kernel with a full-width at half-maximum of 8 mm.

A canonical hemodynamic response function was used for analyzing event-related responses (Friston et al., 1998). The BOLD response to each event type was modeled by convolving a series of delta functions corresponding to the onset of each event with canonical hemodynamic response function. For each participant, all response outcomes (life time 1-5 and frequency 1-5) were modeled as separate conditions. A whole-volume voxel-wise approach was used to identify linear trends in BOLD signal that tracked participants' ratings in each task. These trends were probed in a conjunction analysis (Nichols, Brett, Andersson, Wager, & Poline, 2005). Statistical significance was established using control for false discovery rate ($p < .05$).

3.3   Results

3.3.1   Behavioral Results

The lifetime familiarity ratings of different participants correlated highly with each other (mean $r = 0.53$; $SD = 0.06$ across 100 items). We also observed a significant positive

relationship between participants' ratings and the five levels (i.e., bins) of normative concept familiarity (McRae et al., 2005) that were used to generate our lists (mean $r = 0.66$, $SD = 0.07$, $p < .001$; see Figure 3.2a). For the frequency task probing recent exposure, ratings of relative frequency of experimental exposure showed a significant positive relationship with the five levels of repetition frequency used in the study phase (mean $r = 0.40$, $SD = 0.13$, $p < .001$; see Figure 3.2a), revealing sensitivity to our frequency manipulation at study, and by extension, some validity of these judgments.
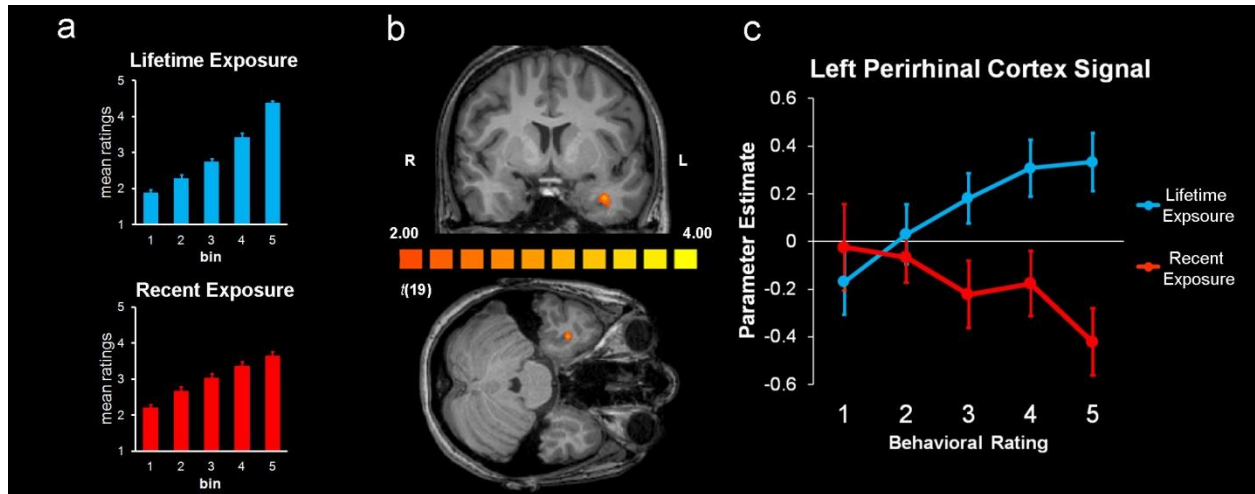
Figure 3.2. Behavioral and fMRI results. (a) Cumulative lifetime familiarity ratings and frequency ratings of recent exposure as a function of normative estimates of lifetime exposure and of recent exposure during the study phase, respectively. See Methods for number of repetitions that correspond to the 5 frequency bins. Behavioral ratings on both tasks were correlated with experimental manipulations. (b) Left PrC region identified in the conjunction analysis. (c) Beta plot for this left PrC region (extracted at FDR $p < 0.05$). Error bars reflect SEM. Left PrC tracks behavioral ratings with a BOLD response that follows opposite directions in both tasks.

3.3.2   Neuroimaging Results

In the fMRI literature on recognition-memory, a decrease in PrC signal is the most commonly reported response that is associated with judged recent exposure to meaningful verbal stimuli (e.g., Daselaar, Fleck & Cabeza, 2006; Henson, Cansino, Herron, Robb & Rugg, 2003; see Kim et al., 2013 for review). Accordingly, we predicted that the judged frequency of recent exposures would be negatively correlated with BOLD signals in PrC. For cumulative long-term exposure, directional predictions are more difficult to make based on published fMRI data. However, neurophysiological recordings in non-human primates have revealed PrC neurons that exhibit a gradual increase in responding over the course of weeks of testing, with hundreds of stimulus repetitions, when animals perform recognition memory tasks (Hölscher, Rolls & Xiang, 2003; Rolls, Franco & Stringer, 2005). This increase contrasts with the classic repetition suppression response that is typically observed as a consequence of recent exposure within experimental sessions (Fahy, Riches & Brown, 1993; Li, Miller & Desimone, 1993; Miller, Li & Desimone, 1991; Xiang & Brown, 1998). While the mapping of repetition effects in single-cell recordings onto fMRI BOLD signals remains incompletely understood (see Grill-Spector et al., 2006), we note that evidence from local field potentials, i.e., physiological signals that have been closely linked to fMRI BOLD responses (Logothetis et al., 2001), also suggests that long-term familiarity of objects, accumulated over many sessions, is reflected in a response increase in monkey inferotemporal cortex (Anderson, Mruczek, Kawasaki & Sheinberg, 2008). Accordingly, we predicted that the perceived long-term familiarity of object concepts would be positively correlated with BOLD signals in PrC, effectively leading to opposite directions of change in signal for both types of memory judgments.

A whole-volume voxel-wise analysis that tested for a significant conjunction of these two linear trends (i.e., with logical operator 'and'; Nichols, Brett, Andersson, Wager & Poline, 2005) offered a powerful way to examine our predictions in a single test across all experimental conditions (i.e. response options). The only brain region that showed the typical decrease in signal for recent exposure in combination with an increase in response for long-term exposure was a portion of left PrC in the anterior collateral sulcus. Activity in this region survived statistical control for false-discovery rate ($p < .05$) and remained the only region

showing a significant effect even when a lenient criterion of $p < .05$ (uncorrected) was applied for the conjunction (see Fig. 3.2b). Notably, when the linear contrasts for each task were examined in isolation, there were no additional clusters in PrC, nor within neighboring antero-lateral temporal or temporo-polar cortex (see Binney et. al, 2010; Skipper et al., 2011; Wright et al., 2015, for potential role of these structures in conceptual processing) that showed a linear trend in either direction. The linear task contrast for judgments of lifetime familiarity did, however, reveal other regions outside the anterior temporal lobe that showed an increase in signal with perceived increases in exposure to object concepts. These regions included several structures that have previously been implicated in recognition memory based on recent exposure (see Kim, 2013, for review), such as the hippocampus, medial prefrontal and medial parietal cortex (see Figure 3.3).
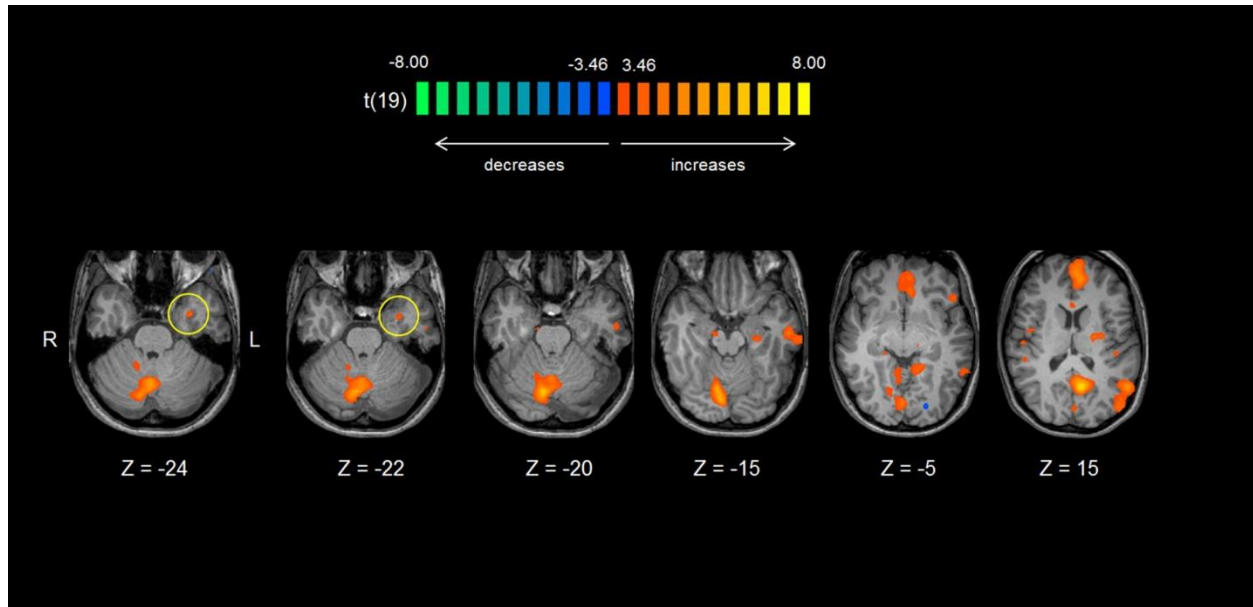
Figure 3.3. Additional regions co-activated with left PrC (circled in yellow) that show linear increases in BOLD response related to perceived long-term exposure to object concepts (linear contrast thresholded at FDR $p < 0.05$).

3.4   Discussion

The present study revealed that the role of human PrC in recognition of prior occurrence extends to the assessment of cumulative lifetime familiarity of object concepts. Our fMRI experiment identified a left PrC region that tracked both perceived frequency of recent laboratory exposure and the perceived lifetime familiarity of object concepts. Notably, left PrC was the only structure that showed the predicted signal change in opposite directions for both types of memory judgments.

Past fMRI research on the role of PrC in recognition memory has typically built on paradigms that required memory decisions with respect to recent item encounters in an experimentally controlled study phase (see Kim et al, 2013, for review). Findings from this research have linked item-based recognition to differential PrC responses for previously studied as compared to novel items (see Diana et al., 2007; Eichenbaum et al., 2007; Kim, 2013 for reviews). Several studies have reported a negative relationship between confidence in the perceived 'oldness' of test items, a behavioural marker that is often assumed to track recent changes in familiarity or item-based memory strength (Yonelinas, 2001), and the PrC BOLD response (Daselaar et al., 2006; Gonsalves et al., 2005; Montaldi et al., 2006; Wang et al., 2014). It is worth noting that the task that revealed a strikingly similar graded decrease in PrC response in the current study, i.e., frequency judgments for degree of recent laboratory exposure, has also been suggested to rely on assessment of item-based memory strength (Hintzman & Curran, 1994; see Hintzman, 2004, for contribution of other processes). Moreover, evidence from research in neurological patients has shown that focal anterior temporal-lobe lesions can produce impairments in frequency judgments for recently encountered study items (Duke et al., submitted; Stanhope & Kopelman, 1998; but see Smith & Milner 1988).

Although our fMRI study identified a region in left PrC that tracked both recent as well as cumulative lifetime experience with object concepts, this finding does not imply, considering the limited spatial resolution of fMRI, that both types of information are carried by the same neurons. Indeed, Xiang and Brown (1998) noted that PrC neurons differ in their sensitivity to effects of recent versus long term exposure when monkeys perform recognition

memory tasks. They reported that some PrC neurons (termed 'recency neurons') respond to repetition of a recent (i.e., within-session) stimulus encounter; this response was observed regardless of whether the stimulus in question had previously been seen in many other sessions distributed over multiple as days (see also Fahy, Riches & Brown, 1993; Li, Miller & Desimone, 1993; Miller, Li & Desimone, 1991; but see Thome et al. 2012). Other PrC neurons identified by Xiang and Brown (1998) responded to whether stimuli had been encountered frequently on prior days, regardless of whether they were seen for the first or the second time in the current session ('familiarity neurons'). Emerging evidence from pharmacological manipulations hints that this differential sensitivity to exposure over different time scales may be linked to distinct mechanisms of synaptic plasticity (see Brown et al., 2012, for review). It is worth noting, however, that in prior neurophysiological work, long-term familiarity signals in PrC were observed in the absence of any behavioral requirement to judge exposure along this dimension across multiple sessions (Fahy, Riches & Brown, 1993; Hölscher, Rolls & Xiang, 2003, Xiang & Brown, 1998). In the current fMRI study, by contrast, participants made explicit judgements of cumulative lifetime exposure to object concepts, allowing us to reveal the relevance of graded PrC signaling for behavior.

The present findings add to a growing body of evidence that links human PrC to the processing of object concepts in task contexts other than recognition-memory judgments for recent study encounters. Several prior fMRI studies have relied on priming paradigms in which repeated exposure to object concepts led to changes in PrC signals in semantic tasks that made no reference to these repetitions (Dew & Cabeza, 2011; Heusser et al., 2012; O'Kane et al., 2005; Voss et al. 2009; Wang et al., 2010; Wang et al., 2014). Past fMRI research has also implicated human PrC in processing of object concepts in tasks that did not involve any manipulation of item repetition, including naming and judging the presence of specific semantic features (Bruffaerts et al., 2014; Clarke & Tyler, 2014; Liuzzi et al., 2015). In the latter set of studies, it has been shown that PrC carries information that is of particular relevance for making fine-grained distinctions among similar object concepts. This evidence provides support for models of PrC functioning that do not argue for a dedicated role in memory processing, but instead emphasize a broader role in feature integration that is also critical for online representation of objects in perceptual tasks (Clark & Tyler, 2015; Cowell et al., 2010; Graham et al., 2010; Murray & Bussey, 1999; O'Neil et al.,

2012). Behavioral findings suggest that increases in concept familiarity are typically associated with increases in feature knowledge that can be gained from repeated object encounters in different episodic contexts. Thus, an important topic for further research is to determine whether the increase in PrC response that we observed in association with perceived lifetime familiarity shows any relationship to differential engagement of processes of feature integration. Regardless of the outcome of such future research, the current findings provide new evidence that extends PrC's role in processing object concepts beyond its well established role in recognition of recent occurrence.

Footnote (1). We conducted a supplementary behavioral experiment in a separate group of healthy young participants (n= 31), in which we asked participants to judge not only lifetime familiarity but also the amount of knowledge they have for specific object concepts (again using items taken from McRae, Cree, Seidenberg, & McNorgan, 2005). The two types of ratings were obtained in separate blocks of the experiment. Analyses of the resulting data revealed a strong positive correlation (across items $r = .54$, $p < .05$, averaged across participants) between perceived lifetime familiarity and estimated knowledge.

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Chapter 4

4   Associative Priming and Lifetime Familiarity Judgements

4.1   Introduction

In the recognition memory literature, item recognition, or familiarity assessment, is most commonly investigated by employing study-test recognition memory tasks. In this type of experiment, participants assess the recent incremental change in familiarity that occurs as a result of a discrete experimental study presentation. Familiarity-based recognition is characterized by a sense of past experience with a stimulus, but with no reported recovery of contextual detail about that study encounter (Yonelinas, 2002). Interestingly though, the majority of studies that have assessed familiarity-based recognition employ meaningful stimuli such as words or pictures of common objects as memoranda (Eichenbaum etal., 2007; Kim, 2013). These stimuli are associated with a varied history of cumulative experience across thousands of individual experiences. The human literature on familiarity-based recognition memory has tended to ignore this aspect of "familiarity" with object concepts and instead the experiments have primarily probed recent incremental changes in familiarity rather than absolute or cumulative levels (Mandler, 1980; but see Coane et al., 2011; Bridger et al., 2014). The main consideration in past recognition experiments of pre-experimental familiarity has been to match lists of old and new test probes on word frequency to minimize the impact of pre-experimental familiarity on old/new decisions for a recent experimental encounter.

Interestingly, these two sources of familiarity have been shown to interact in recognition memory tests. In the 'mirror effect', high frequency words (e.g., bed or house) presented as lures at test are more likely to be falsely judged as having been presented in the study phase (i.e., false alarm), relative to low frequency words. By contrast, low frequency words presented during the study phase are associated with a higher subsequent hit rate at test (i.e., correct 'old' response) than are high-frequency words (Balota & Neely, 1980; Glanzer & Adams, 1990; Joordens & Hockley, 2000; Reder et al., 2000; Coane et al., 2011). The increased false-alarm rate for high frequency words is thought to result from the word having a high level of pre-experimental familiarity, and the effect on low-frequency words results

from a higher level of attention that is afforded to these stimuli due to their relative novelty (Joordens & Hockley, 2000; Reder et al., 2000). Importantly, the confusion between a signal of high pre-experimental familiarity and a feeling of recent incremental familiarity suggests that these forms of mnemonic assessment could share a common cognitive or even neural mechanism.

Findings from the semantic memory literature indicate that humans can judge the cumulative familiarity of object concepts (i.e., the concrete object that a word or picture refers to; Martin, 2015) they have encountered over their lifetime across varied episodic contexts. Interestingly, there is considerable consistency in participants' lifetime familiarity judgements in normative studies of concept knowledge (Cree & McRae, 2003; Moreno-Martinez et al., 2014; Schröder et al., 2012). This is likely due to the fact that, within a shared environment and cultural context, humans encounter many objects at similar frequencies across different forms of media (e.g., printed texts, online), on television, or in face-to-face physical interactions. Importantly, external validity of the observed consistency is reflected in a moderate correlation between objective word frequency and subjective lifetime familiarity ratings (Cree & McRae, 2003). Despite these demonstrations of consistency and validity, however, very little is known about the neural and cognitive mechanisms that allow humans to make lifetime-familiarity judgements for object concepts.

Recent investigations in our laboratory have suggested that lifetime familiarity judgements rely on neural mechanisms in the temporal lobe that also play a role in familiarity-based recognition decisions for recent experimental exposures (Bowles et al., submitted; Duke et al., submitted). In Chapter 2, lifetime familiarity judgements for a large set of object concepts were found to be abnormal in a patient with a left anterior-temporal lobe lesion that included the perirhinal cortex (PrC) but spared the hippocampus. Moreover, a functional magnetic resonance imaging (fMRI) study in healthy young adults demonstrated that a region in left PrC tracked perceived degrees of lifetime familiarity as well as perceived frequency of recent experimental exposure of object concepts (Chapter 3). These findings add to an emerging literature highlighting PrC as a region that processes the semantic feature structure of object concepts in many task contexts (Bruffaerts et al., 2013; Clarke & Tyler, 2014; Wright et al., 2015). Taken together, such findings suggest that PrC is critical for the

assessment of cumulative lifetime familiarity of object concepts but also serves as a region that processes the semantic features of object concepts that have been learned through extensive cumulative life experience.

With respect to cognitive mechanisms, a question that remains unanswered is whether cumulative lifetime familiarity judgements do indeed involve conceptual processing or whether perhaps they are based on the familiarity of surface features such as the orthographic characteristics of printed words denoting concrete nouns. This is not a trivial question given that normative estimates of lifetime familiarity moderately correlate with printed word frequency. Put another way, as of now, it is unclear whether lifetime familiarity judgements can be considered conceptual, or whether other signals accrued through cumulative experience with an object concept could convey the degree of prior exposure independently of access to a semantic representation.

Recent work in fMRI has tied familiarity-based recognition and conceptual fluency together as having a common neural basis, demonstrating that PrC may contribute to the processing of object concepts in task contexts other than recognition-memory judgments for recent experimental study encounters. Several prior fMRI studies having taken advantage of priming paradigms in which repeated exposure to object concepts led to changes in PrC signals in semantic tasks that made no reference to these repetitions (Dew & Cabeza, 2011; Heusser et al., 2012; O'Kane et al., 2005; Voss et al. 2009; Wang et al., 2010; Wang et al., 2014). It has been shown that PrC activity relates to the level of behavioural priming of responses in category-exemplar generation tasks (Wang et al., 2010) as well as natural/manmade judgements (Heusser et al., 2012). In an interesting demonstration of the potentially shared neural mechanism between the recognition of recent experimental presentation and conceptual fluency more broadly, Wang et al. (2014) found that activity reductions in PrC accompanied both recognition memory judgements and the influence of conceptual priming on free association judgements. Some researchers have suggested that conceptual fluency may be a primary variable modulating the decreases in BOLD signal seen in fMRI experiments (Dew & Cabeza, 2013; Voss et al., 2009). For example, it is possible that the tendency for participants to produce conceptually-related words during a free

association test may be due to the heightened level of conceptual fluency resulting from the presentation of a related word in the study phase.

Interestingly, familiarity-based recognition memory has been shown to be influenced by priming manipulations that increase the conceptual fluency of recognition test items (Rajaram & Geraci, 2000; Dew & Cabeza, 2013; see also Taylor et al., 2013). For example, the presentation of an associatively related prime word before old/new recognition judgements for a different memory probe increases the tendency for participants to judge both old and new words as familiar, as indexed by 'know' responses in the remember-know paradigm (Rajaram & Geraci, 2000). Relevant to the current study, Dew and Cabeza (2013) found that associatively-related prime words that were presented during a scanned retrieval phase in the study-test paradigm significantly increased the tendency of participants to attribute familiarity to old and new test words, similarly to Rajaram and Geraci (2000). When investigating the neural correlates of this behavioural effect, they discovered that recognition trials accompanied by a conceptually-related prime word were associated with a decrease in BOLD signal in PrC relative to unprimed trials. In the semantic priming literature, associative primes have also been shown to reduce the response latencies of lexical decisions and categorization decisions about object concepts (Hutchison, 2003). A natural next question emerging from the reviewed literature showing PrC involvement in lifetime familiarity judgements, semantic memory tasks, as well as recognition judgements, is whether lifetime familiarity judgements actually require conceptual processing.

In the current study, we sought to test the idea that cumulative lifetime familiarity judgements require conceptual processing by taking advantage of an associative priming manipulation. Towards this end, associatively-related prime/target word pairs were derived from a large normative database of word associations (Nelson et al., 1998). In this task, participants hear a word and are asked to produce the first word that comes to mind (e.g., producing 'cat' when the cue is 'dog'). We predicted that presentation of associative primes, as compared to unrelated prime words, immediately prior to judgments of cumulative lifetime familiarity for object concepts would decrease response latencies for these judgements. Additionally, based on the findings reported by Rajaram and Geraci (2000) for incremental

familiarity as probed with the remember-know task, we also predicted that associative priming would increase the perceived lifetime familiarity of object concepts.

4.2   Methods

4.2.1   Participants

Forty-one participants took part in the current study (Mean age = 19.4, *SD* = 1.7, 18 males, 23 females). This research was approved by the internal Ethics Board of the Department of Psychology at Western University.

4.2.2   Materials

Two hundred, eighty concrete concepts, derived from a large normative database of concepts (McRae et al., 2005), were selected as targets to be judged for lifetime familiarity (e.g., *HAMMER*). Two lists of 140 concepts were chosen carefully such that there was a continuous distribution of rated normative familiarity as indicated in the McRae et al. (2005) database. One list served as target words for the related prime condition and the other for the unrelated prime condition. Critically, the level of normative concept familiarity (i.e., lifetime familiarity) was matched between each list to allow for the later investigation of priming effects on the perceived familiarity of each target concept. A prime word was chosen for each target word based on free association probabilities in the University of South Florida Free Association Norms database (Nelson et al., 1998). Associative relatedness is represented in the Nelson database according to the production frequencies of words in relation to a cue word from a large-scale free association task. For example, if given the cue word *dog*, a commonly produced associate would be *food*. In order for the cue word to be chosen as a prime, it had to have the highest forward cue-to-target strength (FSG) value for a given target word. FSG values represent the proportion of participants from the free association task who produced a word in relation to the presented cue. To find unrelated prime words, a given cue word was required to have an FSG value of 0 with the target word to which it was assigned.

Across a two-version counterbalance scheme, unrelated primes were paired with 140 target words in version A, whereas in version B related primes were paired those target words. Likewise, the 140 target words paired with related primes in version A were used as

targets in the unrelated prime condition in version B. Both lists A and B were matched with respect to FSG (M_a = 0.29, SD_a= 0.25; M_b= 0.30, SD_b = 0.27), target normative familiarity as indicated by McRae et al. (2005) (M_a = 6.18, SD_a= 1.89; M_b = 6.18, SD_b = 1.89), target letter length (M_a = 5.60 letters, SD_a = 1.91 letters; M_b = 5.68 letters, SD_b = 1.86 letters), target syllable length (M_a = 1.72 syllables, SD_a = 0.80 syllables; M_b = 1.72 syllables, SD_b = 0.81 syllables), as well as prime letter length (M_a = 5.97 letters, SD_a = 2.24 letters; M_b = 5.61 letters, SD_b = 1.74 letters).

4.2.3   Procedure

All word stimuli were presented on a CRT desktop computer monitor via E-Prime 2.0 (Psychology Tools). Participants read instructions on the computer screen. They were informed that concepts would be presented as words on the screen and that they were to rate the familiarity of each concept on a 1-9 scale with 1 meaning 'not at all familiar' and 9 meaning 'highly familiar'. More specifically, they were told that a concept should be considered highly familiar if they have a great deal of experience with it and even encounter it every day perhaps. Four practice trials were provided for participants to become acquainted with the nature of the trial structure. Trials began with a fixation cross that remained at the center of the computer screen for 2000ms. After the fixation cross disappeared, a warning signal (#########) appeared for 500ms (see Figure 4.1 for trial structure). A related or unrelated prime word was presented after the warning signal for 150ms and was immediately followed by the target word (presented in upper case) to be judged for familiarity. Ratings were to be provided within 3000ms via a keyboard press. Timing parameters were chosen based on the timing of Rajaram and Geraci (2000). Related or unrelated prime trials were randomized across the sequence of all trials for every participant.
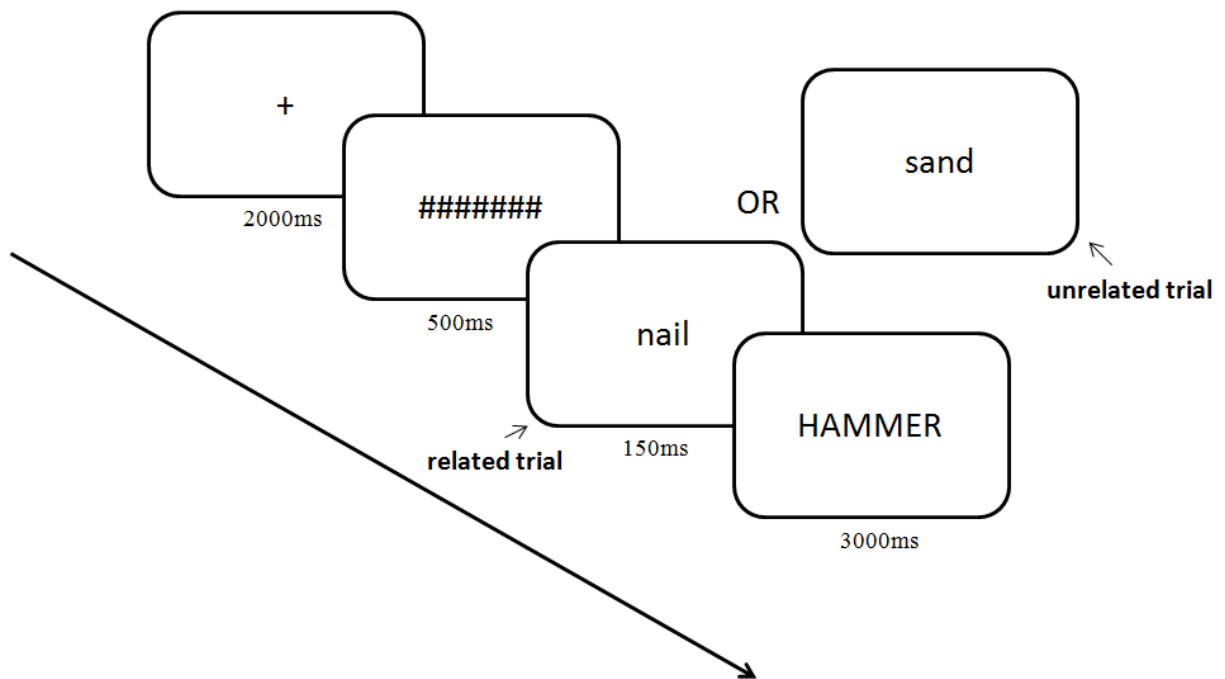
Figure 4.1. The trial structure of the procedure is illustrated. An example of a lowercase related and unrelated prime trial is demonstrated. Target words are presented in uppercase, and are the words judged for lifetime familiarity.

4.3   Results

4.3.1   Response Latencies

First, to determine whether associatively-related primes affect the response latencies of lifetime familiarity judgements, a direct comparison of the mean response latencies was performed between the unrelated and related prime conditions (Figure 4.2). As predicted, mean latency for lifetime familiarity ratings in the related prime condition was significantly shorter relative to the unrelated prime condition (related $M = 1,483$ ms, $SD = 290$; unrelated $M = 1,507$ ms, $SD = 293$; $t(40) = 3.94$, $p < .0001$). To get a sense of the magnitude of priming on response latencies, I calculated a difference score for each participant's (i.e., unrelated Mean reaction time – related Mean reaction time), such that the speeding of response times would be reflected in a positive value. Across participants, the Mean of this priming score was found to be 24 ms, with a Standard Deviation of 39.7 ms with a range of priming scores between -51.4 ms and 107.9 ms across participants.

It was important in the current experiment to match the level of normative lifetime familiarity for the target words in the related and unrelated prime conditions to investigate possible priming effects due to prime/target relatedness. In the current set up, though, the lifetime familiarity of the prime words themselves was not matched between the related and unrelated prime conditions prior to testing. It is possible that a relatively higher level of familiarity for the prime words may have influenced response latencies. To test this possibility, ratings of lifetime familiarity were obtained for the prime words used in the experiment in a sample of 19 healthy young adults. Many of the words used as primes were not included in the McRae et al. (2005) database, warranting the collection of norms from a sample of participants not included in the priming study. Across both versions of the experiment, the mean rated familiarity for related primes was actually lower than for unrelated primes (related $M = 5.49$, $SD = 1.56$; unrelated $M = 6.26$, $SD = 1.39$). This difference was significant across the 19 participants who provided ratings ($t(18) = -9.40$, $p < .0001$). Given that the lifetime familiarity ratings provided were higher for the unrelated primes used in the experiment, this result argues against any interpretation that the level of familiarity of the primes themselves can explain the effects we see on familiarity judgements.
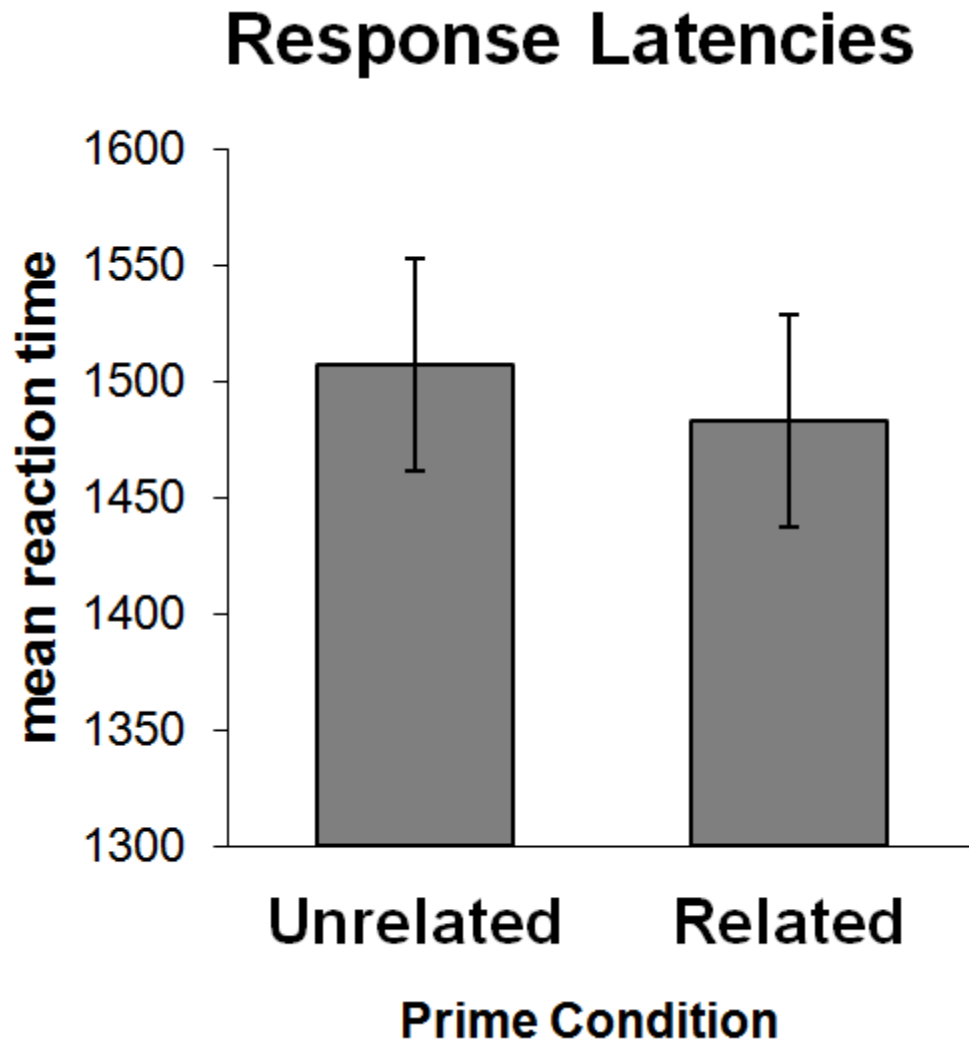
Figure 4.2. Mean reaction time for the unrelated and related prime conditions. Lifetime familiarity ratings were faster for object concepts preceded by an associatively related prime. Error bars represent the standard error of the mean (SEM).

4.3.2   Perceived Lifetime Familiarity Ratings

Next, motivated by findings in the recognition memory literature that associatively-related primes presented during retrieval can boost the perceived incremental familiarity of a target word with respect to presence in a recent study phase, I aimed to determine whether primes similarly affected lifetime familiarity judgements. I first compared the mean rated lifetime familiarity ratings between the related ($M = 5.26$, $SD = .53$) and the unrelated prime condition ($M = 5.23$, $SD = .55$), which did not differ ($t(40) = -1.02$, $p > .3$; see Figure 4.3). One possible reason prime-target relation did not influence the magnitude of familiarity ratings is that some prime-target pairs had a level of associative relatedness that was too weak. To further probe for any differences, I restricted my analysis to related trials with at least an associative strength value of FSG = .10. This cut-off was chosen to increase the strength of association across items included in the analysis, but also to allow for a sufficient number of trials to uncover differences (over 90 items in each prime condition). Critically, I chose a sample of concepts in the unrelated condition that was matched in normative familiarity as determined by McRae et al.'s (2005) database. I again compared the mean rated lifetime familiarity between the related ($M = 5.65$, $SD = .58$) and the unrelated prime condition ($M = 5.53$, $SD = .68$), and this difference was significant ($t(40) = 2.48$, $p < .05$; see Figure 4.4). Again, to get a sense of the magnitude of priming across participants, a difference score was calculated for each participant between the mean related familiarity ratings and unrelated ratings and averaged across participants ($M = .12$, $SD = .30$). The range of priming values was between -.39 and .74).
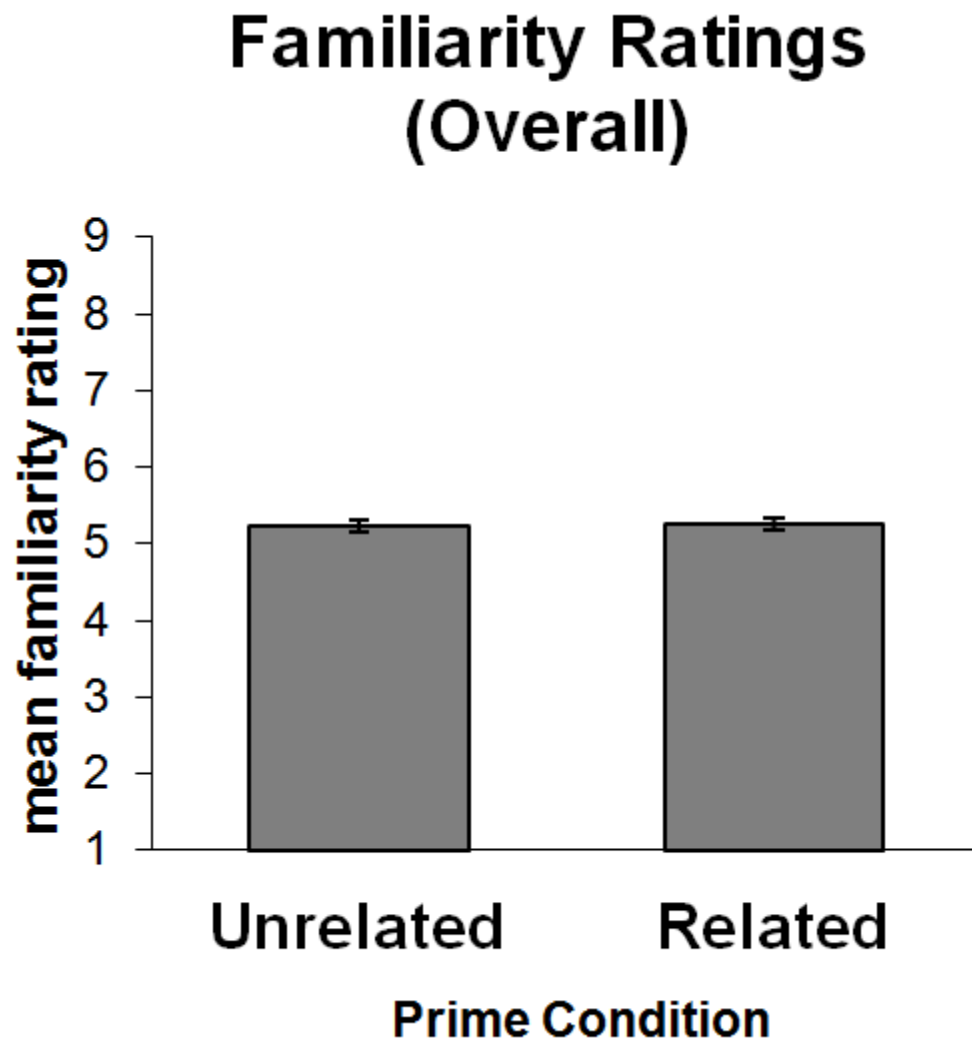
Figure 4.3. Mean lifetime familiarity ratings for the unrelated and related prime conditions. Error bars represent the standard error of the mean (SEM).
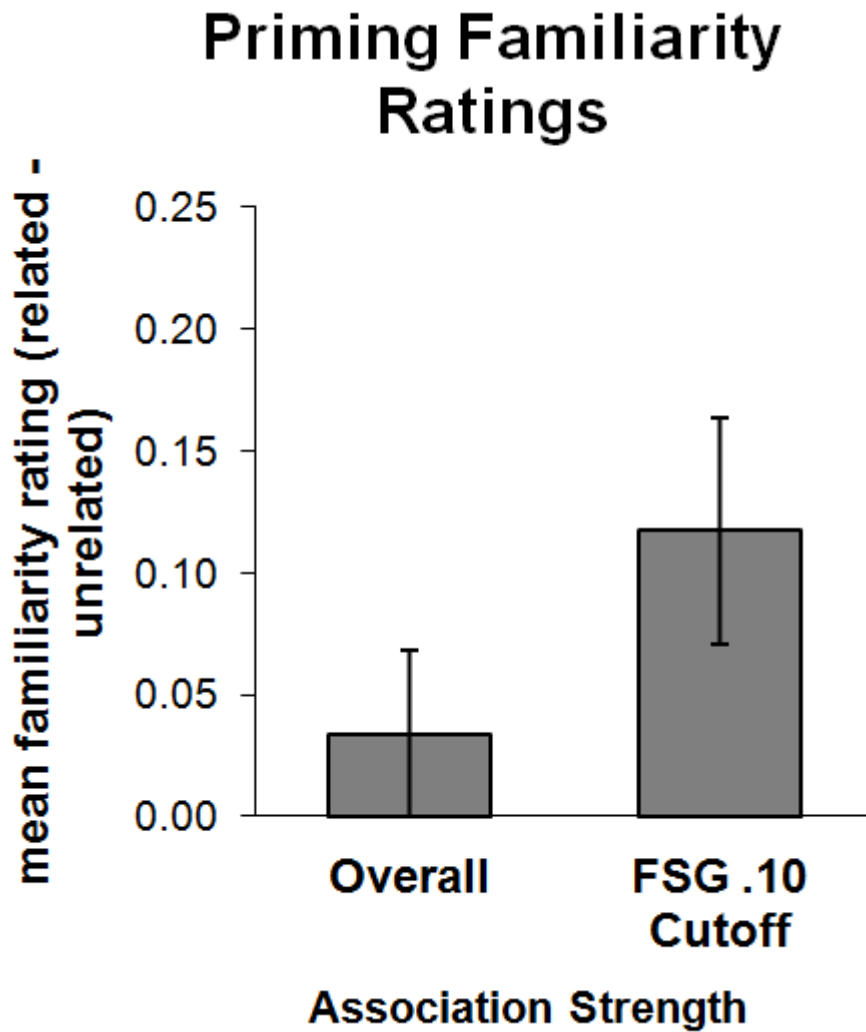
Figure 4.4. Priming of lifetime familiarity ratings. The mean familiarity rating for the unrelated prime condition was subtracted from the mean familiarity rating for the related prime condition. Priming scores are separated by the items chosen for the analysis. All items were used in the 'overall' condition and items with a high level of associative strength were included in the 'FSG .10 Cutoff' condition. Error bars represent the standard error of the mean (SEM).

4.4   Discussion

In the current experiment, associative priming influenced both the response latencies of lifetime familiarity judgments as well as the perceived level of experience expressed in a quantitative rating. More specifically, participants' familiarity ratings were faster when the judgement was preceded by a related prime word relative to an unrelated prime word. Additionally, when a subset of concepts with a relatively high level of prime-target associative strength was chosen, the effects of primes extended to the perceived level of familiarity for an object concept itself. The perceived lifetime familiarity that a participant felt in relation to a concept was higher on average than when the concept was preceded by a related prime compared to trials with an unrelated prime. The effects on lifetime familiarity judgements in the current experiment highlight that these mnemonic judgements involve some level of conceptual processing. Moreover, the manner in which associatively-related primes increased the perceived lifetime familiarity of primed object concepts is consistent with the known effects of these primes on judgements of recent incremental familiarity that result from a discrete experimental study presentation (Rajaram & Geraci, 2000; Dew & Cabeza, 2013). In addition to the studies in Chapters 2 and 3 demonstrating that these judgements of past experience rely on the PrC, it is possible that these old/new recognition decisions and lifetime familiarity share a common neural mechanism that fundamentally relates to the sensitivity of both judgements to conceptual fluency.

The effects of associative primes in the current experiment are consistent with the reported effects of these types of primes in study-test recognition memory experiments. Rajaram and Geraci (2000) found that feelings of familiarity for a recent laboratory exposure to a word can be modulated by the presence of associatively-related primes. More specifically, participants judged old and new test words as having been presented in the study phase more so when, at retrieval, the target was preceded by a related prime. The authors argued that this effect resulted from an increased level of conceptual fluency with recognition test items. In the current experiment, the perceived lifetime familiarity of object concepts also increased when a related associative prime preceded this judgement. Critically, for this effect to be present, the value of associative strength between primes and targets had to be taken into consideration. Interestingly, the cut-off value for associative strength (FSG) that was

incorporated to examine trials involving high levels of prime/target relatedness is similar to the minimum cut-off level used in past experiments in study-test recognition memory experiments that have revealed effects of associatively related primes on recognition decisions (Rajaram & Geraci, 2000; Dew & Cabeza, 2013). Perhaps it is the case that the level of associative strength between primes and targets must exceed a minimum threshold to affect the perceived familiarity of target concepts, and the strength of association in the overall set of concepts may not have been sufficient to influence perceived familiarity itself.

The results of the current study are consistent with recent fMRI work showing an involvement of PrC in task contexts that involve conceptual processing without an explicit assessment of an encounter with object concepts (Dew & Cabeza, 2011; Heusser et al., 2012; O'Kane et al., 2005; Voss et al. 2009; Wang et al., 2010; Wang et al., 2014). Even though participants are required to make an assessment of graded levels of past experience with an object concept for lifetime familiarity judgements, the retrieval of a specific pertinent episode relating to that item is not necessary. The results in the current experiment, taken together with the findings from Chapters 2 and 3, strongly suggest that old/new recognition decisions and lifetime familiarity share a common neural basis (i.e., PrC) that relates to the sensitivity of both judgements to conceptual fluency. Similar suggestions have been put forth concerning the common role of PrC in processing conceptual fluency in both explicit (e.g., study/test recognition) and implicit (e.g., priming of related free associates) memory (Dew & Cabeza, 2011). Future work will be needed to determine how conceptual fluency resulting from associative primes influence PrC activity in relation to lifetime familiarity judgements.

The current results strengthen the assertion that the cumulative assessment of lifetime familiarity for object concepts can be related to judgements of recent incremental changes in familiarity in the study-test recognition memory paradigm. The common effects of associative primes on familiarity-based recognition responses in the study-test paradigm (Rajaram & Geraci, 2000; Dew & Cabeza, 2013) and cumulative lifetime familiarity judgements in the current study suggest that these judgements may share a common cognitive mechanism. This assertion is consistent with the connection that has already been made in studies showing the 'mirror effect' in recognition. This effect shows that a signal of pre-

experimental familiarity for concepts can be confused for a feeling of having seen a concept recently in the study phase of a recognition memory experiment. If both a recent incremental familiarity signal and a cumulative familiarity signal are similar at a phenomenological level, conceptual fluency induced by associative primes would affect both of these judgements in a similar manner. It would be interesting in future research to determine whether the recent presentation of object concepts can lead to an increased sense of cumulative lifetime familiarity.

Lifetime familiarity judgements preceded by related primes were also found to be faster than judgements preceded by unrelated primes. This result is consistent with the effects of associatively-related primes on semantic judgements of categorization (Rips et al., 1973; Hutchison, 2003). The priming affect on response latencies in the current experiment provides an initial piece of evidence that cumulative lifetime familiarity assessment is a judgement that requires conceptual processing. It is unclear based on the current results to what extent these judgements require conceptual processing. While a lifetime familiarity judgement is one that requires assessing an object concept that has been instilled with meaning across one's lifetime, it is still a judgement of the relative magnitude of presentation frequency of an object concept. The assessment of the magnitude of experience with an object concept, presumably, can occur somewhat independently of the knowledge you have stored about it. In some ways, lifetime familiarity assessment is still a cumulative recognition judgement. Future research will be needed to clarify to what extent lifetime familiarity assessment is related to the perceived knowledge one feels they have in relation to an object concept.

Future research will be needed to determine to what extent primes chosen based on the amount of feature overlap they have with target concepts can affect lifetime familiarity judgements. Researchers in semantic memory have suggested that the types of relationships that are preserved between primes and targets may come from any number of different sources when they are determined based on associative norms (Moss et al., 1995). For example, some proportion of associative strength may be related less to the underlying semantic structure of a concept, but instead, may reflect phrasal associations in language. Williams (1996) found that associative relatedness can represent categorical similarities (e.g.,

cat-mouse), functional relations (e.g., knife-fork) as well as property relations (e.g., camel-hump). Given the uncertainty concerning what types of relationships are captured by primes derived from association norms, it is a necessary next step to perform a similar experiment with prime-target relatedness reflecting the amount of shared features between these two concepts. Not only is this important when trying to determine whether lifetime familiarity judgements are conceptual in nature, but it will also be helpful to further connect lifetime familiarity judgements to the growing literature demonstrating that the PrC processes information relevant to the feature structure of object concepts (Bruffaerts et al., 2013; Clarke & Tyler, 2014; Wright et al., 2015). If indeed lifetime familiarity judgements critically rely upon PrC computations, and can be influenced by associatively-related primes in behavioural experiments, feature-based primes should also affect them. For the purposes of the current investigation into whether cumulative lifetime familiarity judgements can be considered conceptual in nature, the use of associatively-related primes is useful.

4.5   References

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Chapter 5

5 General Discussion

5.1 Summary of Goals and Findings

The recognition of previous experiences with objects in our environment is a critical mnemonic ability that guides behaviour in an adaptive manner. To date, research in the domain of recognition memory has centered primarily on investigating the ability to assess recent incremental changes in familiarity that result from discrete laboratory exposures (Mandler, 1980). Furthermore, research in the cognitive neuroscience of memory has extensively centered on an investigation of the neural correlates of item-based recognition, and has highlighted the PrC as an MTL that critically contributes to this ability. While recognizing that an object has been encountered recently in a discrete episode is important, the world in which we live is characterized by varied cumulative histories of experience with objects that are imbued with meaning, and this meaning has accumulated over many individual episodic encounters. Even in everyday colloquial use of the concept "familiarity", we rarely refer to a feeling of oldness that we get from seeing a word in a shopping list, rather, we use the term to denote varied levels of lifetime experience that aggregates over hundreds if not thousands of individual episodes that contain meaningful interactions with objects. The current project addressed whether the PrC is involved in the assessment of such cumulative levels of familiarity with object concepts. It was informed by neurophysiological studies in non-human primates suggesting that some neurons in PrC track cumulative long-term exposure to simple line drawings over the course of days and weeks (Hölscher et al., 2003). Moreover, it was motivated by fMRI studies that revealed that the representational structure of PrC activity closely resembles the feature structure of meaningful objects even in task contexts that do not require judging past experience with those objects (Bruffaerts et al., 2014). To test whether PrC's functional role in processing of object concepts includes the assessment of their cumulative levels of lifetime familiarity, I conducted a set of experiments in patients with varied MTL lesion profiles and completed an fMRI study with closely matched task requirements in healthy individuals. In addition, I employed a behavioural

priming paradigm to shed light on cognitive mechanisms involved in lifetime familiarity judgements.

In Chapter 2, I directly probed the role of the left anterior temporal lobe, which includes PrC, in cumulative lifetime familiarity assessment in patient NB. Patient NB and a group of healthy control participants judged their level of lifetime familiarity with a large set of 541 concrete concepts. Using a correlation-based approach, it was revealed that NB's familiarity judgements were less correlated with control participants than those of the controls were with each other. In fact, NB had a lower mean correlation in ratings relative to every single control participant, strongly suggesting that her lifetime familiarity judgements are abnormal in nature. Her abnormality was most noticeable in concepts that have a high level of feature overlap with other concepts (e.g., living things). In another experiment, this effect was replicated even when picture cues were provided, suggesting that NB's abnormalities are not specific to orthographic stimuli. Under these circumstances, again, her abnormalities were most pronounced for objects that are known to have a high level of feature overlap with other concepts. Next, I aimed to contrast the effects of an extra-hippocampal lesion that spared the hippocampus (patient NB) with an extensively-studied patient who has a lesion to the hippocampus and extended-hippocampal system but not PrC (patient HC) in order to gain insight into the anatomical specificity of the abnormal lifetime familiarity effect observed in NB. As predicted, patient HC showed no differences in performance as compared to a separate age- and education-matched healthy control sample, suggesting that the functional integrity of the hippocampus is not necessary to make normal cumulative familiarity judgements. Linking these findings back to familiarity resulting from controlled laboratory exposures, NB and healthy controls were also tested on a frequency judgement task that required judging the relative frequency of presentation of words from an extended study phase. As predicted and mirroring the results for cumulative lifetime familiarity, NB was impaired in judging the frequency of presentation of stimuli from the study phase. Given that NB's lesion included extensive damage to structures in the ATL, it is difficult to conclusively tie the effect of abnormal lifetime familiarity assessment to PrC based on these patient-based experiments alone. To shed further on anatomical specificity in the processing of lifetime familiarity, in Chapter 3, healthy young adults made these judgements while undergoing fMRI. In addition to lifetime familiarity judgements, graded frequency judgements were

required for a different set of concepts, which allowed us to compare BOLD signal changes associated with assessment of a recent incremental change in familiarity and cumulative lifetime familiarity judgements. A region in the left anterior collateral sulcus that is part of PrC was found to track both the perceived frequency of recent laboratory exposure as well as the perceived lifetime familiarity of object concepts. Interestingly, the trajectory of these linear trends followed opposite directions with an increased sense of lifetime familiarity being characterized by higher levels of activity in left PrC, and an increased sense of presentation frequency being associated with lower levels of activity in this same region. No other region of the lateral or polar ATL that was included in patient NB's lesion demonstrated this effect. In fact, this pattern of activity, revealed by a conjunction analysis of both linear trends, was present in only one area of the scanned brain volume, namely left PrC. As such, these results complement the findings in patient NB and point more conclusively to left PrC as being a region that is critically important in the graded assessment of cumulative lifetime experience with object concepts.

To gain a better understanding of the cognitive basis of lifetime familiarity judgements, in Chapter 4, I made use of an associative conceptual priming paradigm. The primary question I addressed was whether lifetime familiarity judgements require conceptual processing or whether, perhaps, other sources of information (e.g., orthographic familiarity) could be sufficient to judge familiarity. To get at this question, I presented associatively related primes supra-liminally prior to the assessment of lifetime familiarity for concrete object concepts. The familiarity ratings and response latencies of these ratings were compared to those for a separate list of concrete concepts that were preceded by unrelated prime words. In support of my hypothesis, response latencies were significantly faster when concepts were preceded by a semantically related prime relative to concepts preceded by an unrelated prime. In addition to effects on response latencies, the perceived cumulative familiarity of concepts increased when a related prime was presented prior to the judged concept. This effect on the perceived familiarity itself was most pronounced for trials with strong associative links between primes and targets. The results of this priming experiment thus provide evidence for the idea that judging a concept's lifetime familiarity requires conceptual processing at some level. Together with the findings presented in Chapters 2 and 3, these results suggest that PrC supports cumulative lifetime familiarity judgements based on access to conceptual

representations that were likely acquired and refined through a lifetime of object exposures across many episodic contexts.

5.2   Familiarity and Conceptual Processing in PrC

The results presented in Chapter 4 highlight that lifetime familiarity judgements require some level of conceptual processing. Not only did associatively-related primes boost the level of perceived lifetime familiarity for object concepts, they also resulted in significantly shorter rating latencies. These results are consistent with previous findings in the recognition memory literature showing that associative primes increase the perceived level of recent incremental familiarity in the study-test paradigm (Rajaram & Geraci, 2000; Dew & Cabeza, 2013). Studies making use of associative primes in the recognition literature have interpreted the increase in perceived recent exposure as resulting from a heightened level of conceptual fluency for trials accompanied by a conceptually-related prime. Conceptual fluency can be defined as the ease of processing of a particular object concept (Rajaram & Geraci, 2000). The congruent conceptual content between the prime and target words is thought to be taken as a signal that target words have been encountered in the recent past. The results from Chapter 4 suggest, perhaps, that conceptual fluency is a highly relevant dimension of lifetime familiarity judgements as well. It is conceivable that graded levels of exposure to object concepts throughout one's lifetime manifests as similarly graded levels of conceptual fluency, and may serve as the basis of lifetime familiarity judgements when conceptually-related primes are absent.

In a recent fMRI experiment, Dew and Cabeza (2013) demonstrated that associatively-related prime words that were presented during a scanned retrieval phase in the study-test paradigm significantly increased the tendency of participants to attribute familiarity to old and new test words. When isolating the neural correlates of this behavioural effect, they discovered that trials accompanied by a conceptually-related prime word were associated with a decrease in BOLD signal in PrC relative to unprimed trials. When applying these findings to the fMRI results presented in Chapter 3, it is somewhat unclear why fluency effects in Dew & Cabeza (2013) would be associated with activity decreases in PrC and the BOLD effect associated with lifetime familiarity would be characterized by a graded increase in activity in

PrC. Either this argues against the idea that conceptual fluency serves as the primary basis of lifetime familiarity judgements, or it is possible that conceptual fluency can exacerbate the activity decrease associated with judgements of recent incremental familiarity in the study-test paradigm as well as activity increases in lifetime familiarity judgements. This idea would require further testing to be further elaborated. In other words, it is a possibility that the activity decrease in PrC in Dew and Cabeza (2013) is specific to task contexts that require judgements of recent incremental familiarity.

The patient findings in Chapter 2 and the neuroimaging findings in Chapter 3 add to a growing body of evidence that links human PrC to the processing of object concepts in task contexts other than recognition-memory judgments for recent study encounters. Across two experiments, NB made lifetime familiarity judgements that were abnormally correlated with well-matched healthy control participants. These results, taken in combination with the linear trends in BOLD signal found in a portion of left PrC that was damaged in patient NB, strongly supports the notion that PrC carries signals about cumulative prior item exposure over extended time periods. These results contribute to a growing body of evidence suggesting that PrC is engaged in tasks that do not require the explicit assessment of a recent exposure to that concept in an experimental study phase (Dew & Cabeza, 2011; Heusser et al., 2012; O'Kane et al., 2005; Voss et al. 2009; Wang et al., 2010; Wang et al., 2014). In this literature, it has been shown that PrC activity relates to the level of behavioural priming of responses in category-exemplar generation tasks (Wang et al., 2010), natural/manmade judgements (Heusser et al., 2012), as well as the speeding of living/non-living judgements based on previous experimental exposures (Voss et al., 2009). It is important to note that many of these effects have been interpreted in the context of increased conceptual fluency that results from a recent experimental exposure to that concept (Voss et al., 2009) As is the case with these types of semantic tasks, judgements of lifetime familiarity do not require that a participant retrieve information related to a recent exposure to that object concept. For example, we immediately know that we have a lower level of familiarity for 'aardvarks' relative to 'dogs', and the data in amnesic patient HC presented here hint that this does not require bringing to mind specific episodic memories involving aardvarks, which may have only occurred one or two times at zoos across the entire span of our lives. The potential role of recollection in lifetime familiarity judgements is discussed in greater depth below.

Lifetime familiarity judgements do differ in one important way from the above-cited group of experiments that have highlighted a role of PrC in semantic task contexts that do not require an assessment of past experience with object concepts. Even though an assessment of lifetime experience with object concepts does not require the conscious retrieval of individual encounters, it is still a judgement of past experience with a concept-at-hand. As such, one may be able to place lifetime familiarity judgements somewhere between an explicit assessment of a past individual experimental study encounter (i.e., recognition memory) and judgements considered to be "purely" semantic as mentioned above (i.e., naming, category production). The primary distinction between recognition memory judgements in the study-test paradigm and lifetime familiarity judgements is that the latter requires tapping into an aggregate signal of many individual past encounters. Even though the current findings add to an existing literature showing PrC involvement in tasks that do not require an explicit appreciation of an encounter in a recent study phase, they contrast with findings from these studies in that they still require reflection on the history, rather than the outcome of this past experience. For example, categorization decisions do not require an explicit assessment of the magnitude of past exposure to a concept, they require that you know what many individual encounters have taught you about a concept.

5.3 Semantic Representations, Feature Overlap and Judgements of Lifetime Familiarity

The current results raise the interesting question of whether the assessment of past experience with object concepts builds upon the same representations in PrC that allow for making semantic judgments about object concepts. Is the representation that allows for a living/non-living judgement on aardvarks the same representation that is used in the assessment of cumulative levels of lifetime experience? Recent theoretical and computational work on the interface between the MTL and the ventral visual pathway suggest this may indeed be the case (Graham et al., 2010; Murray & Bussey, 1999; Cowell et al., 2010; Clarke & Tyler, 2015). Specifically, it has been proposed that PrC can be seen as an extension of the ventral visual pathway, rather than a structure that plays a dedicated role in declarative memory functioning, with a specific role in object processing in task contexts that require discrimination of complex objects characterized by a large number of shared features.

Theorists in this literature have opted to interpret the role of PrC functioning in terms of the nature of the representation it supports rather than with respect to the presence or absence of mnemonic demands. According to this view, any task that requires disambiguation of objects characterized by a complex conjunction of features that they share with other objects will engage PrC. While much of the pertinent empirical work has focused on perceptual feature overlap (Barense et al., 2007; O'Neil et al., 2009; Lee et al., 2008; Bussey & Saksida, 2007; Erez et al., 2013), more recently, conceptual feature overlap has also been considered (Bruffaerts et al., 2014; Clarke & Tyler, 2014; Liuzzi et al, 2015; Wright et al., 2015). These studies have shown that PrC is a brain region that disambiguates objects with high feature overlap in the service of naming and concept feature verification. Such a representational account provides a useful overarching theoretical characterization of PrC function that can account for the current thesis results as well. Specifically, PrC may play a critical role in judgments of lifetime familiarity because such judgments require disambiguation of objects concepts with conceptual and perceptual feature overlap.

That NB's abnormalities in these judgments are sensitive to the degree of feature overlap, as shown in Chapter 2, provides particularly strong support for this account. The results in patient NB suggests then that disambiguating object concepts that have many shared features with other object concepts may be a prerequisite process that precedes or accompanies cumulative lifetime familiarity assessment. However, inasmuch as I found that PrC directly tracks degree of prior exposure (Chapter 3), in a recent study phase as well as over the lifetime, the current findings still point to PrC as a declarative memory region as well, in the sense that it carries information about the history of experience that can be 'declared' in familiarity judgements. One outstanding question relates to whether NB's abnormality manifests phenomenologically as a confusion of the object concept at hand, or as a noisy cumulative familiarity signal that accompanies the processing of the item. It is also worth noting that the degree of abnormality in patient NB's ratings was not such that she did not correlate at all with the ratings provided by healthy controls, but a significantly lower degree of correlation, which may suggest that her abnormalities are not readily obvious to her.

A potentially important research question that emerges from the effects of feature overlap in the reviewed research is whether the PrC is involved in the initial build-up of conceptual feature structure in semantic memory. It is possible that the PrC only processes this type of information after learning has taken place. Most, if not all, patients with PrC damage that have been studied, including patient NB, have had a lesion to PrC only after the initial learning of concepts has taken place. It would be interesting in future fMRI work to observe how PrC processes new object learning that is experimentally controlled. This could be accomplished by having healthy participants gain experience in the laboratory with novel artificial objects characterized by high or low feature overlap with other novel objects. Furthermore, it would also be interesting to have patient NB learn novel object features in the same manner to determine whether her abnormalities are at the level of assessing object concepts with high feature overlap that have already been learned or whether this abnormality extends to the accrual of new object information. Put differently, is it the case that patients with PrC damage will have anterograde impairments in encoding object-specific information, much like a patient with bilateral hippocampal damage has anterograde amnesia for episodes that take place after the onset of their damage? Given the often diffuse nature of MTL lesions that researchers tend to have access to, an investigation into the build-up of experience with individual objects will likely have to be related to degrees of overlapping PrC damage across a large sample of patients.

5.4   Relation to Findings in Non-Human Primates

Taken at face value, the results presented in Chapters 2 and 3 may tempt one to argue that we are tapping into the human equivalent of 'recency' neurons and 'familiarity' neurons that have been discovered in monkey PrC (Fahy et al., 1993; Hölscher et al., 2003; Xiang & Brown, 1998). More specifically, is it possible that the diverging linear trends in BOLD activity for frequency judgement task and cumulative lifetime familiarity task are directly manifesting as a result of 'recency' neurons and 'familiarity' neurons respectively? It is impossible to know based on the findings from patient NB and the fMRI study in healthy individuals whether we are indeed measuring the differential contributions of the same types of neurons in human PrC for a number of reasons. Considering the limited spatial resolution of fMRI, where potentially hundreds of thousands if not millions of individual neurons are

contained in a single measured voxel, it is not possible to directly link the opposing BOLD signal trends found in the fMRI experiment presented in Chapter 3 to the findings from Hölscher et al. (2003). It will be important in future research, perhaps with patients with temporal lobe epilepsy who undergo intracranial recordings in the context of surgical planning, to test whether there is an similar profile of 'recency' and 'familiarity' neurons in PrC when individuals perform the tasks employed in my fMRI study. Regardless, taken together the diverging linear trends in my fMRI experiment and the different types of neurons described in neurophysiological recordings converge to suggest that PrC carries distinct sources of information about recent incremental and cumulative long-term exposure.

A point worth noting is that in prior neurophysiological research, long-term familiarity signals in PrC were observed in the absence of any behavioral requirement to judge cumulative exposure across multiple sessions (Fahy et al., 1993; Hölscher et al., 2003; Xiang & Brown, 1998). In the current thesis research, we observed abnormalities in NB's performance while she was required to make explicit judgements about cumulative lifetime exposure to object concepts. Furthermore, we found graded BOLD signals in left PrC in Chapter 3 in relation to the subjective familiarity responses. It will be important in future research to determine to what extent subjective feelings of lifetime experience drive activity in PrC relative to activity that may objectively track experience with stimuli. Towards this end, an experimental set up similar to Hölscher et al. (2003) could be implemented, but in humans. For example, artificial objects could be presented in a continuous recognition paradigm during fMRI scanning. In this type of set up, objects are presented multiple times with many intervening objects and participants are required to judge whether objects are old or new. As objects are repeated dozens of times, it would be possible to track how PrC activity changes as participants are exposed to artificial objects that are recognized consciously or not. In addition to this test of recent exposure, other objects could be pre-familiarized in a session prior to fMRI scanning to determine how PrC responds to artificial objects that have been presented to participants hundreds of times over previous days. As in the current set of thesis experiments, participants could also judge their overall level of familiarity with objects from a time that was not limited to one exposure on the current scanning day. It would be interesting to determine whether PrC responds only in situations

accompanied by conscious retrieval, or if it also tracks exposure similarly when exposure is high, but not accompanied by conscious recognition.

5.5   Role of Recollection in Lifetime Familiarity Judgements

Considering that much of the current thesis research has been influenced by research in cognitive neuroscience that has attempted to disentangle the contributions of recollection and familiarity to recognition memory, it is important to consider what role, if any, recollection may play in lifetime familiarity judgements. It is entirely possible that the recollection of specific episodes pertinent to a given object concept may occur spontaneously during the assessment of cumulative lifetime familiarity, but whether this recollection contributes to lifetime familiarity judgements themselves is an outstanding question. For example, I may spontaneously recollect how easy it was to get out of bed this morning when assessing the familiarity of the word 'bed'. While it is clear that the task does not require any recollection or any reference to a specific encounter it is possible participants engage in recollection regardless. Whether recollection plays a role in lifetime familiarity judgements warrants consideration in light of evidence that has implicated hippocampal involvement in apparently semantic tasks, such as object naming or conceptual fluency, i.e., the speeded generation of exemplars from different semantic categories (Klooster & Duff, 2015; Greenberg et al., 2009; Ryan et al., 2008; Sheldon & Moscovitch, 2013; Westmacott & Moscovitch, 2003; Whatmough & Chertkow, 2007). Building on the widely held view that the hippocampus plays a critical role in binding items to episodic contexts (Cohen & Eichenbaum, 1993), such evidence has led to the suggestion that episodic and semantic memory may interact even on tasks that do not require any recollection, and that recollection of a relevant autobiographical episode can help generate or retrieve semantic information (see Sheldon & Moscovitch, 2012, for detailed discussion). Importantly, the associative priming paradigm used in Chapter 4 highlights that lifetime familiarity judgements are indeed affected by primes that are associatively related. Given that these judgements are influenced by associated concepts in semantic memory, the spontaneous retrieval of associated concepts or episodes is a possibility.

If the recollection of a specific encounter with an object contributes in a significant manner to lifetime familiarity judgements, we would expect that patients with a dense autobiographical recollection impairment might reveal such an influence. Indeed, the strongest source of evidence in this thesis that speaks to whether recollection plays a role in lifetime familiarity judgement comes from the final experiment of Chapter 2, in which HC, a patient with bilateral hippocampal lesion was required to make lifetime familiarity judgements for object concepts. HC demonstrated normal familiarity ratings despite her well-documented autobiographical memory impairment (Kwan et al., 2010; Rosenbaum et al., 2011). This is a striking result because HC's autobiographical memory impairment has been revealed even under conditions in which the names of object concepts were used as cues for episodic retrieval in the Galton-Crovitz task (Kwan et al., 2010). The finding that patient HC made cumulative familiarity judgements in a manner that correlated highly with a carefully selected group of matched control participants provides strong support for the notion that a normally functioning recollection mechanism is not required to make normal lifetime familiarity judgements. This pattern of results suggests a functional distinction between the recollection of the time and place of particular autobiographical object encounters, and the assessment of degrees of experience over hundreds or thousands of encounters across different episodic contexts.

5.6   Future Directions

The results presented in the current thesis research are critically important to models of PrC functioning for both the semantic memory and recognition memory literatures. I argue that the results can not only extend models of PrC function within each of these fields of study on their own, but may also serve to bridge our theoretical understanding of why PrC would be involved in conceptual processing and in the assessment of recent incremental changes in familiarity that result from discrete exposures to objects in our environment.

It will be important in the future to clarify why assessing graded recent incremental familiarity and cumulative lifetime familiarity were characterized by differential trajectories of graded BOLD signal in PrC in Chapter 3. It has been shown in past research in the study-test paradigm that "old" responses were associated with less activity that items judged to be

new, but it is not apparently obvious why feelings of heightened cumulative lifetime familiarity would be marked by an increase in PrC activity. As mentioned previously, it will be important to know whether the pattern of activity characterized by the conjunction analysis that incorporated both frequency and lifetime familiarity judgements relates at all to different functional neurons in the PrC, akin to the findings from Xiang & Brown (1998) or Hölscher et al. (2003). Not only is this an important question with respect to clarifying whether non-human primate PrC tracks experience similarly with human PrC, it will help inform the question presented earlier of whether the representation utilized for semantic memory tasks is the same as that used to assess recent incremental familiarity or cumulative lifetime familiarity. At a cognitive level, it is known that a concept's pre-experimental familiarity can be confused as a recent laboratory encounter in the study-test paradigm (Glanzer & Adams, 1990), suggesting perhaps, that if there exist 'recency' and 'familiarity' neurons in the human brain, they may interact. First, we would at least need to know whether 'recency' and 'familiarity' neurons discovered in non-human primates map onto the recent incremental familiarity and cumulative familiarity construct to begin with. It would be very useful to investigate the 'mirror effect' in recognition in patients with implanted PrC electrodes. For example, if recognition trials were to be sorted according to a word's pre-existing familiarity (i.e., word frequency), it would be possible to determine how neurons respond differently to a recent incremental exposure between words with low and high pre-experimental familiarity. Unfortunately, it is incredibly difficult to come across these kinds of patients.

With respect to the findings from Chapter 2 on patient NB and HC, larger patient samples will be needed to be able to more conclusively tie PrC functioning as being necessary for lifetime familiarity judgements. In the current thesis, the strength of the conclusion that PrC critically contributes to lifetime familiarity assessment comes as a result of complementary studies using both a patient-based approach and neuroimaging. In order to claim that PrC functioning is necessary for proper cumulative lifetime familiarity assessment via patient evidence alone, a larger sample of patients with variable ATL lesion profiles is required. Towards this end, we are currently collaborating with researchers at Baycrest Hospital in Toronto to begin testing patients with mild cognitive impairment (MCI) on the frequency and lifetime familiarity tasks. Some recent research has been devoted to investigating estimates of recollection and familiarity in patients with MCI, and has offered

insights into the neural correlates of these two processes (Westerberg et al., 2006; Westerberg et al., 2013).

A natural extension to the behavioural priming experiment from Chapter 4 would be to test the effects of using prime/target pairs that are determined based on their level of feature overlap. Considering the finding in Chapter 4 that conceptually-related primes can affect the perceived familiarity of object concepts as well as the response latencies to make the judgement, one would predict that a prime that shared features with the target word to-be-judged should also affect these judgements. A more theoretically-driven reason why feature-based primes would be expected to affect lifetime familiarity judgements emerges from the literature showing that a region that affects these judgements, left PrC, houses information about the feature structure of object concepts (Bruffaerts et al., 2014; Clarke & Tyler, 2014; Liuzzi et al, 2015; Wright et al., 2015). Moreover, the finding that patient NB's abnormal familiarity judgements were most noticeable in a group of concepts characterized by high feature overlap lends credit to the prediction that feature-based primes would be worth testing.

Further, in terms of a cognitive investigation of the nature of lifetime familiarity judgements, it will be useful to determine to what extent episodic recollection is present during familiarity assessment, and to what extent the contents of recollection can inform a familiarity judgement. One possible way that this may be achieved is to incorporate a modified version of the remember-know procedure and directly ask, on a trial to trial basis, whether a specific episodic encounter was contemplated during the cumulative familiarity judgement. Perhaps it is the case that judgements accompanied by specific recollections will act to boost the perceived familiarity of the object concept because it is interpreted as evidence of experience. This speculative account of the effects that recollection may play will need to be tested in future research that builds on the findings reported in this thesis.

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and recency in regions of the anterior temporal lobe. *Neuropharmacology, 37*, 657-676.

Appendices

Appendix A: Documentation of ethics approval

Please give a copy of both the protocol and the letter of approval to Daniella, Room 7416, SSC [ext. 84690] for the department's records. We are required to keep copies.

Thank you

'chology The University of Western Ontario
Room 7418 Social Sciences Centre,
London, ON, Canada N6A 5C1
Telephone: (519) 661-2067Fax: (519) 661-3961

Western

Use of Human Subjects - Ethics Approval Notice

Review Number	12 12 02	Approval Date	12 12 05
Principal Investigator	Stefan Kohler/Devin Duke	End Date	13 07 01
Protocol Title	Semantic memory and familiarity		
Sponsor	n/a		

This is to notify you that The University of Western Ontario Department of Psychology Research Ethics Board (PREB) has granted expedited ethics approval to the above named research study on the date noted above.

The PREB is a sub-REB of The University of Western Ontario's Research Ethics Board for Non-Medical Research Involving Human Subjects (NMREB) which is organized and operates according to the Tri-Council Policy Statement and the applicable laws and regulations of Ontario. (See Office of Research Ethics web site: http://www.uwo.ca/research/ethics/)

This approval shall remain valid until end date noted above assuming timely and acceptable responses to the University's periodic requests for surveillance and monitoring information.

During the course of the research, no deviations from, or changes to, the protocol or consent form may be initiated without prior written approval from the PREB except when necessary to eliminate immediate hazards to the subject or when the change(s) involve only logistical or administrative aspects of the study (e.g. change of research assistant, telephone number etc). Subjects must receive a copy of the information/consent documentation.

Investigators must promptly also report to the PREB:
a) changes increasing the risk to the participant(s) and/or affecting significantly the conduct of the study;
b) all adverse and unexpected experiences or events that are both serious and unexpected;
c) new information that may adversely affect the safety of the subjects or the conduct of the study.

If these changes/adverse events require a change to the information/consent documentation, and/or recruitment advertisement, the newly revised information/consent documentation, and/or advertisement, must be submitted to the PREB for approval.

Members of the PREB who are named as investigators in research studies, or declare a conflict of interest, do not participate in discussion related to, nor vote on, such studies when they are presented to the PREB.

Clive Seligman Ph.D.

Chair, Psychology Expedited Research Ethics Board (PREB)

The other members of the 2012-2013 PREB are: Mike Atkinson (Introductory Psychology Coordinator), Rick Goffin, Riley Hinson Albert Katz (Department Chair), Steve Lupker, and TBA (Graduate Student Representative)

CC: UWO Office of Research Ethics
This is an official document. Please retain the original in your files

Curriculum Vitae

EDUCATION

2011-present   **University of Western Ontario**, London, Ontario

> Ph.D. program in Behavioural and Cognitive Neuroscience (in progress)

> Advisor: Dr. Stefan Köhler

2009- 2011   **University of Western Ontario**, London, Ontario

> M.Sc. in Behavioural and Cognitive Neuroscience, 2011 (completed)

> Advisor: Dr. Stefan Köhler

2004-2008   **University of Arizona**, Tucson, Arizona

> B.A. in Psychology and German Studies, 2008 (completed)

> Graduated *Summa Cum Laude;* Cumulative GPA: 3.92

PUBLICATIONS

Beukema, S., Cruse, D., **Duke, D**., Naci, L., Fernandez-Espejo, D., Osborne, N., Gonzalez-Lara, L. E., Clement, J.S., Owen, A.M. Accurate memory after recovery from the vegetative state. (Submitted).

Bowles, B., **Duke, D.**, Martin, C.B., Rosenbaum, R. S., McRae, K., Köhler, S. Role of left perirhinal cortex in assessing the cumulative long-term exposure to object concepts. (Submitted). *BB and DD made equal contributions to paper.

Duke, D., Ethridge, P., Safronsky, E., & Köhler, S. Fear enhances familiarity-based recognition for faces. (Submitted).

Duke, D., Bowles, B., Gilboa, A., Rosenbaum, R. S., McRae, K., Köhler, S. Abnormal semantic memory structure in a case of developmental amnesia. (In preparation).

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MANUSCRIPTS IN PREPARATION

Duke, D., Bowles, B., Gilboa, A., Rosenbaum, R. S., McRae, K., Köhler, S. Abnormal semantic memory structure in a case of developmental amnesia. (In preparation).

CONFERENCE PRESENTATIONS AND PUBLISHED ABSTRACTS

Duke, D., Bowles, B., Martin, C.B., Rosenbaum, R. S., McRae, K., Köhler, S. Human perirhinal cortex supports recent frequency and cumulative long-term exposure to concepts. Poster. London Health Research Day, London, Ontario, April 2015. Poster Award in Neuroscience and Mental Health section ($500).

Fiaconni, C., Barkley, V., Finger, E.C., **Duke, D.**, Carson, N., Köhler, S. Psychophysiological evidence related to delusional person misidentification in neurodegenerative disease. Poster. London Health Research Day, London, Ontario, April 2015.

Duke, D., Bowles, B., Martin, C.B., Rosenbaum, R. S., McRae, K., Köhler, S. Human perirhinal cortex supports frequency judgments as well as judgments of cumulative lifetime familiarity. Poster. Society for Neuroscience, Washington D.C., November 2014.

Fiaconni, C., Barkley, V., Finger, E.C., Carson, N., **Duke, D.**, Rosenbaum, R.S., Gilboa, A., Köhler, S. Nature and extent of person recognition impairments associated with capgras syndrome in lewy body dementia. Society for Neuroscience, Washington D.C., November 2014.

Duke, D., Bowles, B., Gilboa, A., Rosenbaum, R. S., McRae, K., Köhler, S. Abnormal Semantic Memory Structure in a Case of Developmental Amnesia. Poster. Canadian Association for Neuroscience, Toronto, May 2013.

Duke, D., Bowles, B., Gilboa, A., Rosenbaum, R. S., McRae, K., Köhler, S. Abnormal Semantic Memory Structure in a Case of Developmental Amnesia. Poster. Cognitive Neuroscience Society, San Francisco, April 2013.

Duke, D. & Köhler, S. Effects of affective priming on familiarity-based recognition of faces. Poster. Association for Psychological Science, Chicago, IL, May 2012.

Duke, D., Safronsky, E. & Köhler, S. Effects of affective priming on the familiarity-based recognition of faces. Poster. Lake Ontario Visionary Establishment, Niagara, Ontario, Canada, February 2012.

Duke D., Lin C-Y, Kawa K., Nadel L., Ryan L. Distinguishing the roles of the parahippocampal cortex and hippocampus during object-scene recognition. Poster. Cognitive Neuroscience Society, Montreal, June 2010.

Duke D., Hayes S., Glisky E., Ryan L. Recognition of objects in a manipulated context scene. Abstract submitted, Arizona Alzheimer's Consortium Annual Meeting, Phoenix, AZ, May 2007.

Duke D., Hayes S., Glisky E., Ryan L. Recognition of objects in a manipulated context scene. Poster presented at the 20th Annual Spirit of Inquiry Research Forum, Tucson AZ, February 2007.