COGNITIVE NEUROSCIENCE METHODOLOGIES PROVIDE INSIGHT INTO MEDIAL TEMPORAL LOBE CONTRIBUTIONS TO PERCEPTION, LANGUAGE, AND CREATIVITY

BY

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ABSTRACT

The functional contribution of medial temporal lobe has been studied in the human brain for over half a century. Insight into the nature of this extraordinary structure was discovered when epileptic patient H.M. had an experimental operation to surgically resect his bilateral medial temporal lobes. The procedure resulted in profound anterograde amnesia, demonstrating the critical role of medial temporal lobe in forming new long-term memories; yet a variety of other capacities remained intact (e.g., intelligence, personality, and skills). The notion that medial temporal lobe function was isolated to the formation of new long-term memories persisted for several decades until the development of new methodologies. It has been the endeavor of cognitive neuroscience to further our understanding of the structural organization of complex cognition and behavior.

The focus of this dissertation is to provide evidence supporting the functional contribution of medial temporal lobe sub-regions, namely perirhinal cortex and hippocampus, to a variety of capacities classically considered outside the domain of memory. Several studies are presented that demonstrate the contribution of these regions to certain aspects of perception, language, and creativity. In Chapter 3, we investigated the ability of perirhinal cortex to support complex object (i.e. fused) perceptual representations in healthy young adults using a novel approach - functional magnetic resonance adaptation (Rubin, Chesney, Cohen, & Gonsalves, 2013). In Chapter 4, we investigated whether hippocampus and its role in forming arbitrary associations are necessary to form visual and linguistic common ground (Rubin, Brown-Schmidt, Duff, Tranel, & Cohen, 2011). Eye-movements of participants with hippocampal amnesia were monitored during real-time language comprehension. In Chapter 5, we investigated whether hippocampus and its role in flexibly expressing information contribute to creativity (Duff, Kurczek, Rubin, Cohen, & Tranel, 2013). Performance was assessed in participants with hippocampal amnesia on standardized tests of verbal and figural creativity (i.e. Torrance Tests of Creative Thinking). The results from these studies emphasize that there are many areas of cognition, which are typically considered outside the domain of memory, that engage the characteristic processing features of medial temporal lobe. These regions retain their functionality irrespective of timescale and contribute to many complex cognitive functions.

To my Family, you are the ones that inspire me.

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CHAPTER 1: BACKGROUND ON MEDIAL TEMPORAL LOBE (MTL)

Advancements in Characterizing Memory Systems of the Brain

For as long as people have thought about the human mind, they have been interested in the nature of different kinds of memory, and reasonably so, since memory is the substance of thought and behavior that provides a record of our life experiences. The idea that there are different kinds of memory has been contemplated by great thinkers for many centuries. Aristotle contemplated being able to *reminiscence* (i.e. recall the flow of events in unique experiences) vs. experience a sense of *familiarity* (i.e. perceptually-driven memory for previously experienced events) (Eichenbaum, 2010). Scholars like William James distinguished between primary memory and secondary memory, similar to what is now called *short-term memory* (STM) and *long-term memory* (LTM). The notion of memory consolidation and the distinction between STM and LTM led to influential theories, like Hebb's cell assembly theory (Nadel & Hardt, 2010). While some of these ideas continue to be discussed, a move to describe human memory in terms of function-structure relationships initiated the precise characterization of this region's unique contribution to cognition.

In the middle of the 20th century, the first understanding of function-structure relationships came from brain damaged individuals. Brain damage to different parts impaired different kinds or aspects of memory. Russell and Nathan (1946) studied individuals with brain-damage from Second World War and documented the phenomenon of *retrograde amnesia* (RA) (i.e. loss of access to memories formed before events prior to brain injury). The most noteworthy example, arguably, is a particular demonstration of the relationship between memory and the human brain, in which one and only one, experimental surgery was performed to the human *medial temporal lobes*.

The (now famous) patient H.M had intractable epilepsy and seizures that appeared to originate from within his *medial temporal lobes* (MTL). Surgeons tried to alleviate the seizures by removing MTL brain tissue bilaterally. The surgery was successful in that it greatly reduced incidence of his seizures; however, it was tragic in that he now suffered from profound *anterograde amnesia* (i.e. loss of ability to form new everyday memories) and moderate *retrograde amnesia* (Scoville & Milner, 1957). Although the injury was unfortunate, it unmistakably demonstrated the role of MTL (1) in the consolidation (but not storage) of old memories and (2) critically, in forming new memories.

Given the rarity of a patient with such precisely localized brain damage, a tremendous amount of research was done to characterize the spared and impaired abilities of H.M. using a diverse range of neuropsychological assessment tools (Corkin, 1984; Corkin, Milner, & Teuber, 1968) - albeit, many of them considered coarse by today's standard. H.M. performed very poorly on standard tests of LTM, which was not very surprising because he virtually had no memory for everyday events. His deficit in forming new memories was severe; but stood in striking contrast to his intact abilities - his intelligence, personality, language use, perception, skill learning, and even short-term memory, were measured as normal.

Other research on individuals with MTL amnesia also demonstrated differences on measures that indicated impaired LTM and spared STM (Baddeley & Warrington, 1970; Warrington & Baddeley, 1974). These data led to the historical idea that (1) amnesia is a deficit *only* in LTM and (2) MTL damage does not affect STM, causing many to believe that cognitive abilities that take place on the same timescale as STM do not engage MTL.

Researchers set out to more fully characterize MTL and its contribution to long-term memory systems. Lesion work was performed on animals, in combination with more sophisticated neuropsychological testing on humans with MTL amnesia. Insights from animal (e.g. Bunsey & Eichenbaum, 1993; Eichenbaum & Bunsey, 1995; Eichenbaum & Cohen 1988) and human (e.g. Cohen & Squire, 1980) studies led to the theory that MTL damage impairs *declarative memory*, which is episodic (i.e. specific personal experiences) and semantic (i.e. factual knowledge) in nature, and spares *nondeclarative memory*, which is procedural in nature (e.g. skills, priming, simple classical conditioning, habituation) (Cohen & Eichenbaum, 1993; Cohen & Squire, 1980; Squire, 1992; Squire & Zola, 1996). This characterization of multiple memory systems gathered much support (Norman and O'Reilly, 2003; Poldrack & Packard, 2003; Tranel, Damasio, Damasio, & Brandt, 1994; Squire, 2004).

The focus of this dissertation will be on the declarative memory system and using advanced cognitive neuroscience methodologies to characterize the contribution of MTL sub-regions, namely perirhinal cortex and hippocampus, to a diverse set of tasks.

Breakthroughs in Cognitive Neuroscience

Cognitive neuroscience as a field is the study of the biological substrates underlying the mental processes that result in cognition. At a systems level, the field is concerned with how different brain regions contribute to cognition; both in terms of their individual contribution and in terms of how multiple regions interact as a network to facilitate complex thought and behavior. The challenge has been in the development of new methodologies that allow for the noninvasive study of the human brain.

Since the mid to late 20th century, the emergence of an increasingly diverse set of sophisticated methodologies has tremendously increased our understanding of the function-structure relationship in the human brain. Traditional cognitive neuroscience methods include brain imaging (e.g., fMRI - functional magnetic resonance imaging, PET - positron emission topography, and MEG - magnetoencephalography), electrophysiological neural recordings (e.g., EEG - electroencephalography, ERPs - event-related potentials), and neuropsychological patients studies (e.g., individuals with focal brain damage or complex methods of voxel-based lesion-symptom mapping - VLSM). Combinations of these techniques are also used. Occasionally, fMRI and neuropsychological studies incorporate the use of eye-tracking (Hannula, Althoff, Warren, Riggs, Cohen, & Ryan, 2010; Rubin, Brown-Schmidt, Duff, Tranel & Cohen, 2011).

The cognitive neuroscience approaches to studying memory have resulted in a greater understanding of its neural substrates (e.g., Eichenbaum, 2013; Cabeza & Moscovitch, 2013; Milner, Squire, & Kandel, 1998). The experiments in this dissertation use a combination of different cognitive neuroscience approaches to better characterize the functional contribution of MTL sub-regions to different domains of cognition. We used neuropsychological studies of patients with hippocampal amnesia and brain imaging (fMRI) in healthy adults. Previous research undoubtedly shows MTL contributes to forming new long-term memories; but as we discovered, the characteristic processing features of MTL sub-regions contribute to specific aspects of perception, language, and creativity.

Understanding Medial Temporal Lobe Function

In the past few decades there has been much work characterizing the anatomy of human medial temporal lobe (MTL). Findings support several prominent theories that aim to explain the functional contribution of MTL sub-regions, in terms of the kind of memory each region subserves. The main structures in MTL are hippocampus (including CA1-CA3, dentate gyrus, and subiculum), perirhinal cortex, and parahippocampal cortex. Most theories propose that these regions make contributions to ***qualitatively*** different kinds of memory.

Perhaps the most supported theory of MTL function, and one of the earliest, is relational memory theory (Cohen & Eichenbaum, 1993; Eichenbaum & Cohen, 2001). According to relational memory theory, hippocampus (1) supports the binding of <u>**arbitrarily**</u> related, discrete pieces of information, (2) permits the <u>**flexible**</u> expression of information, and (3) links converging inputs from various association cortices. For example, this includes information about co-occurrence of people, places, and objects, along with the <u>spatial</u>, <u>temporal</u>, and <u>interactional</u> relations among them (Eichenbaum & Cohen, 2001). The researchers differentiated relational memory and item memory. Perirhinal cortex and other regions neighboring hippocampus support item memory. Item memory is the binding of **inflexible** relations - i.e. <u>**fused**</u>, unitized or configural representations (Cohen, Poldrack, Eichenbaum, 1997).

Another theory of MTL function also proposes different structures support different kinds of memory, although it distinguishes primarily between the role of hippocampus and perirhinal cortex in recognition memory (Aggleton & Brown, 1999; Brown & Aggleton, 2001). Recognition memory is the capacity to both identify and judge the quality of a prior occurrence (Mandler, 1980). Recognition memory consists of ***qualitatively*** different modes – <u>recollection</u>

and familiarity. Recollection is supported by hippocampus - the experience of 'remembering' – (e.g., *I know I have seen this before because I can remember a specific episode*). Familiarity is supported by perirhinal cortex - the experience of 'knowing' - (e.g., *I know I have seen this before but I do not remember a specific episode*) (Brown & Aggleton, 2001).

A more recent theory of MTL function overlaps conceptually with the role of MTL in episodic memory and relational memory theory, yet emphasizes a different MTL sub-region in representations of *context only memory bindings* (Davachi, 2006; Eichenbaum, Yonelinas, & Ranganath, 2007; Ranganath, 2010). This theory suggests that parahippocampal cortex supports a ***qualitatively*** different kind of memory representation than perirhinal cortex (i.e. *item memory bindings*) or hippocampus (i.e. *item-context memory bindings*).

This binding theory incorporates recent evidence from human neuroimaging studies. (Previous theories relied mostly on evidence from neuropsychological and animal lesion studies). The binding theory is consistent with relational memory theory in describing hippocampus as supporting representations of bindings among items-in-context and perirhinal cortex as supporting specific item representations. The binding theory differs in that it theorizes parahippocampal cortex as supporting distinct representations of context.

There is abundant support for the theories mentioned above that suggest functional specialization within MTL, yet there are others researchers that regard the reported structure differences as ***quantitative***, instead of performing qualitatively different functions (Squire, Stark, Clark, 2004; Squire, Wixted, & Clark, 2007). Many of the observed differences, which have been thought of as differentiating between representations of item vs. relations, and recollection vs. familiarly, actually reflect the strength of the memory - weak vs. strong. Hippocampus does not represent a specific kind of information but rather represents a stronger memory with more information, while perirhinal cortex represents a weaker memory with less information. A stronger memory is likely to contain information about relations between items and recollection of a specific episode, while a weaker memory is likely to contain information about an item not associated with a specific experience.

These theories make distinctions between ***qualitatively*** and ***quantitatively*** different kinds of memory supported by MTL sub-regions. But relational memory theory is unique in that it regards **time** (or <u>temporal</u> order) as any other kind of relation that is supported by hippocampus; no different than space is any other kind of relation supported by hippocampus. Other theories regard MTL function as being specialized for dealing with information about the past; as such the majority of assessments were well designed, but essentially not different from canonical tests of memory – (e.g. present information and then perform test memory on presented information).

A contribution of relational memory theory is that it raises an important question regarding the functional contribution of MTL sub-regions during tasks on much shorter time scales – i.e. seconds or less. The question is: *if hippocampus is critical to (1) binding <u>arbitrarily</u> related pieces of information, (2) permitting the <u>flexible</u> expression of information, and (3) linking converging inputs from various association cortices, then is hippocampus critical for the same functions when the functions occur on the timescale of seconds or less*? In order to answer this question, researchers desired advance methodologies and valuable cognitive neuroscientific evidence.

On the Time Scale of Short-Term Memory

The development of cognitive neuroscience and ever more sophisticated tasks allowed researchers to investigate the question: does medial temporal lobe (MTL) participate during relational tasks that take place on the time scale of short-term memory (STM)? Is hippocampus necessary for binding arbitrary relations and permitting flexible expression of information when the task takes a few seconds?

In the 1990's, the answer to this question was clearly "*No*". The Annual Review of Psychology published an article, "The Structure and Organization of Memory" (Squire, Knowlton, & Musen, 1993, p. 454), which states:

> "*One of the oldest and most widely accepted ideas about memory is that short-term memory (STM) can be usefully distinguished from long-term memory (LTM) (James 1890; Waugh & Norman 1965; Glanzer & Cunitz 1966; Atkinson & Shiffrin 1968). That this distinction is prominently reflected in the organization of brain systems is demonstrated by the fact that amnesic patients have intact STM despite severely impaired LTM (Baddeley & Warrington 1970; Drachman & Arbit 1966; Milner 1971).*"

The idea that (1) amnesia is a deficit *only* in LTM and (2) that MTL damage does not affect STM caused many researchers to believe that cognitive abilities that take place on the timescale of STM do not involve the *same* brain structures essential to LTM.

Does cognitive neuroscientific evidence support the mutual exclusivity of the above statements? Does hippocampus bind arbitrary relations and permit flexible expression of information when the task takes a few seconds? Is hippocampus critical for the same functions when the functions occur *on the timescale of short-term memory*?

Using advanced methods, cognitive neuroscientists investigated these questions with a precision that was never possible before. Specifically, cognitive neuroscientists asked: Is hippocampus necessary for binding arbitrary relations and permitting flexible expression of information when the task takes a few seconds?

The findings were surprising to many. A growing amount of evidence now exists that challenges whether MTL function is limited to the formation of new long-term memories. MTL amnesia and fMRI studies reveal hippocampal involvement during tasks on the time scale of short-term memory, working memory, and during online processing. The relational attributes of the task are thought to involve hippocampal function because deficits are observed in these aspects of the tasks in participants with hippocampal amnesia, relative to neurologically intact comparison participants (Barense, Gaffan, & Graham, 2007; Hannula, Tranel & Cohen, 2006; Olson, Moore, Stark, & Chatterjee, 2006; Olson, Page, Moore, Chatterjee, & Verfaellie, 2006; Watson, Voss, Warren, Tranel, & Cohen, 2013).

Hannula, Tranel, and Cohen (2006) were among the first to demonstrate relational memory impairments in participants with hippocampal amnesia over short delays. The study tested two kinds of relational memory - spatial and non-spatial relations - at short and long delays.

To test spatial relations, participants viewed scenes containing items and were asked about the location of a specific item (to orient them to the identity and location of the item). Then after a lag of 1, 5, or 9, the scene was repeated. Participants were asked (1) if the scene had previously been presented and (2) if any of the items had moved. The last question measured relational memory for spatial relations - (e.g. *was the lamp to the right of the sofa*?)

To test non-spatial relations, a face and scene were presented together. Then after a lag of 1 or 9, a probe trial was presented that displayed a scene with three equally familiar faces. Participants were asked to indicate which face was previously associated with the scene. This question served as a test of relational memory for *arbitrarily* related pieces of information. The task design minimized processing of spatial relations because all faces and scenes were presented in the same spatial position on every trial type.

On both spatial and non-spatial tasks, participants with hippocampal amnesia showed impairments relative to neurologically intact comparison participants at the longest delay – which was no more than a few minutes. Highlighting the expected finding that amnesia was a deficit in long-term memory (LTM).

Surprisingly, participants with hippocampal amnesia also showed impairments relative to neurologically intact comparison participants at the earliest delay – which was no more than a few seconds. An impairment in relational processing was evident from the earliest delays in hippocampal amnesics, and yet no impairment was observed on measures of item processing. Item memory for the scenes showed no difference between groups at the shortest delay. These finding suggest item memory is preserved in hippocampal amnesics that do not also have damage to perirhinal cortex.

Hannula et al. (2006) demonstrates that when task performance depends on relational processing, regardless of whether the critical information is spatial or non-spatial in nature, hippocampus is required to bind arbitrarily related pieces of information and permit flexible expression of information, even when the task takes a few seconds.

Other evidence comes from studies that combine monitoring eye-movements with performance measures of participants with hippocampal amnesia. These studies capture deficits in relational processing that behavioral measures alone may not be sensitive enough to detect. Warren and colleagues observed deficits in participants with hippocampal amnesia during several tasks that involving online relational processing - i.e. tasks in which all the necessary information remained available without an imposed testing delay (Warren, Duff, Tranel, & Cohen, 2010, 2011).

fMRI studies have also provided evidence that suggests hippocampus is involved in processing of relational information even when the task takes a few seconds (Cabeza, Dolcos, Graham, & Nyberg, 2002; Öztekin, McElree, Staresina, & Davachi, 2009; Ranganath, Cohen, & Brozinsky, 2005; Ranganath & D'Esposito, 2001).

The characterization that MTL function is not limited to long-term memory, recognition memory, or episodic memory, is growing in consensus. Articles that review collections of recent studies dispute the historical claim that hippocampal processing is isolated to the formation of new long-term memories. Instead, acknowledging that individual MTL sub-regions contribute to more cognitive functions than previously thought (Cashdollar, Duncan, & Duzel, 2011; Kumaran, 2008; Ranganath & Blumenfeld, 2005).

CHAPTER 2: MTL CONTRIBUTIONS BEYOND LONG-TERM MEMORY

Does MTL Contribute to Perception?

Initial studies of hippocampal amnesia described perception as intact subsequent to medial temporal lobe (MTL) damage, causing early theoretical and experimental work to dismiss the notion that MTL contributes to perception. Now evidence exists that contributions of MTL extend to several cognitive domains, beyond its isolated role in long-term memory (LTM). The functional contribution of individual MTL sub-regions, though, is disputed.

Several cognitive neuroscientists theorize that perirhinal cortex, in particular, contributes to perception, rather than strictly memory processes (Murray, Bussey, & Saksida, 2007; Saksida & Bussey, 2010). These theories extend ideas that emphasize perirhinal cortex as situated at the top of a hierarchically organized *visual* system (not memory system), and suggest it supports representations of visual objects that are built from simple features combined into more and more complex conjunctions (Desimone & Ungerleider, 1989). Under such a view, perirhinal cortex participates in both perception, and memory, of complex/fused object representations (Saksida & Bussey, 2010).

Research focusing on MTL sub-regions suggests different functional contributions to perception (Barense et al., 2007; Bussey & Saksida, 2002, 2005; Graham, Barense, & Lee, 2010; Lee, Barense, & Graham, 2005; Lee, Yeung, & Barense, 2012; Murray et al., 2007). Some neuropsychological findings suggest that the entire MTL, namely hippocampus and perirhinal cortex support perception (Erez, Lee, & Barense, 2012; Lee & Rudebeck, 2010b; Warren, Duff, Jensen, Tranel, & Cohen, 2012; Warren et al., 2010, 2011). Other neuropsychological findings suggest perirhinal cortex is exclusively involved in supporting perception (Barense et al., 2012; Devlin & Price, 2007; Lee & Rudebeck, 2010a; Peterson, Cacciamani, Barense, & Scalf, 2012).

Researchers have also used different cognitive neuroscience methodologies to investigate the functional contribution of MTL to perception. Neuroimaging (i.e. fMRI) findings complement the vast majority of neuropsychological findings to suggest that MTL contributes in complex object and scene discrimination (Barense et al., 2012; Devlin & Price, 2007; Lee & Rudebeck, 2010b; Peterson et al., 2012). Some researchers also measure eye-movements in individuals with MTL amnesia to detect differences in the time-course of MTL involvement during perceptual tasks (Erez et al., 2012; Lee & Rudebeck, 2010a; Warren et al., 2010, 2011); since pure behavioral measures are not as sensitive. Interestingly, one group of researchers does not observe perceptual deficits in individuals with MTL amnesia (Shrager, Gold, Hopkins, & Squire, 2006).

Perception, Perirhinal Cortex, and Fused Object Representations

In Chapter 3, we investigate (1) the contribution of perirhinal cortex to perceptual representations of complex objects that were fused together, (2) the use of fMR-adaptation (fMRa) as a tool capable of indexing the ability of different brain regions to represent fused complex objects, and (3) the idea proposed by relational memory theory that perirhinal cortex supports item memory - the binding of **inflexible** relations - **fused**, unitized or configural representations (Cohen, Poldrack, Eichenbaum, 1997).

In this experiment, we manipulated the particular combination of visual forms that composed an object to bias its perception as either a single fused object or two separate objects.

The critical comparison was between the condition in which the same fused object was presented throughout the duration of the trial (i.e. Fused item condition) to the condition in which a non-fused variant of two visual forms was presented and immediately followed by a fused variant of the same visual forms (i.e. Paired item condition). In this way, the final stimulus was equivalent across conditions - what differed was their viewing history.

fMR-adaptation (fMRa) indexes the ability of different brain regions to represent information of different kinds. The basic logic of fMRa is to record the combined hemodynamic response to a train of stimuli, with the idea that if the same stimulus is repeated each subsequent response will show “adaptation”, and be smaller than the previous response in regions that represent that property of the stimulus. This technique takes advantage of the phenomenon of repetition suppression, which is a general property of neurons in the ventral visual stream at the single-cell and population level (Desimone, 1996; Grill-Spector, Henson, & Martin, 2006).

We expected that perirhinal cortex and late visual areas would demonstrate sensitivity to fused complex object bindings, as revealed by recovery from neuronal adaptation, whereas early visual areas would demonstrate sensitivity to general perceptual similarities, as revealed by neuronal adaptation.

Does MTL Contribute to Language?

Initial studies of hippocampal amnesia described language use as intact subsequent to medial temporal lobe (MTL) damage, causing early theoretical and experimental work to dismiss the notion that MTL contributes to language use. Now evidence exists that contributions of MTL extend to several cognitive domains, beyond its isolated role in long-term memory (LTM). The functional contribution of individual MTL sub-regions, though, is disputed.

Some researchers theorize that there is a functional contribution of MTL to language. MacKay and colleagues analyzed archival data from famous amnesia patient H.M. to construct the node structure and binding theory. Semantic binding node theory suggests that these nodes are required for normal language use, to read and produce syntax, prosody, and semantics of sentences. The researchers are compelled by data from H.M. demonstrating impairments in language use, since they interpret the findings as resulting from damage to semantic binding nodes (MacKay, 2006; MacKay & James 2001).

The declarative/procedural model of language is another theory that characterizes the functional contribution of MTL to language use (Ullman, 2001; Ullman, 2004; Ullman, Corkin, Coppola, Hickok, Growdon, Koroshetz, & Pinker, 1997). Scientists theorize that the declarative model of language involves the mental lexicon, which depends on temporal lobe structures including MTL, and the procedural model of language involves mental grammar, which depends on a network of specific frontal, basal-ganglia, parietal and cerebellar structures.

Although both theories extend the functional contribution of MTL to language, neither one provides sufficient explanation for the pattern of findings observed in neuropsychological language studies of hippocampal amnesia.

Some studies of hippocampal amnesia report spared language abilities, including artificial grammar (Knowlton, Ramus & Squire, 1992), syntactic priming (Ferreira, Bock, Wilson & Cohen, 2008), and referential communication (Duff, Hengst, Tranel & Cohen, 2006), while other studies report impaired language abilities, including reported speech (Duff, Hengst, Tranel

& Cohen, 2007), verbal play (Duff, Hengst, Tranel & Cohen, 2009), and definite article use (Duff, Gupta, Hengst, Cohen & Tranel, 2010).

The pattern of spared and impaired abilities in language studies of hippocampal amnesia is explained mostly by Duff and colleagues (Duff & Brown-Schmidt, 2012; Duff, Hengst, Tengshe, Krema, Tranel, & Cohen, 2008; Duff et al., 2006). Duff and Brown-Schmidt (2012) suggest several fundamental properties of language use that place high demands on hippocampal processing - i.e. that language is an arbitrary system of relations, its use is flexible and creative, its processing is incremental, and it often relies on multi-modal input.

In typical conversational settings, frequent aspects of language such as *common ground*, require high amounts of relational processing. Processing information about co-occurrences of people, places, and objects, along with the spatial, temporal and interactional relations among them, requires the ability to relate arbitrary pieces of information. The ability to bind arbitrary pieces of information depends on hippocampal processing (Eichenbaum & Cohen, 2001).

This view suggests that the degree to which language tasks involve relational processing - i.e. the ability to relate arbitrary pieces of information (Eichenbaum & Cohen, 2001), the expected of contribution of MTL should reveal deficits in individuals with hippocampal amnesia.

Common Ground, Hippocampus, and Arbitrary Relations

The dominant view of common ground is that when individuals encode information about an event, they tag those memories with information about who was there, what was said, and what each person’s role was in the event (Clark & Marshall, 1978, 1981). This view of common ground emphasizes the contribution of declarative memory and relational representations (e.g., information about the co-occurrence of people, places, and objects, along with the spatial, temporal, and interactional relations among them), implicating the involvement of medial temporal lobe (MTL) (Cohen & Eichenbaum, 1993; Eichenbaum & Cohen, 2001).

Competing theories suggest that common ground does not rely on declarative or episodic memory, which indicates that the underlying memory representation is not supported by MTL. Pickering and Garrod (2004) suggest interlocutors align mental models via priming, which results in an implicit representation of common ground, lacking in episodic details. Similarly, Horton and Gerrig (2005a, 2005b) suggest low-level, cue-based associations between partners serve as the basis for much of common ground, which also indicates that the underlying memory representation is not supported by MTL.

In Chapter 4, we examine common ground memory representations in participants with hippocampal amnesia (i.e. a selective deficit in declarative and episodic memory). Eye-movements of participants with hippocampal amnesia are monitored to determine whether hippocampus and its role in forming arbitrary associations are necessary to form visual and linguistic common ground during real-time language communication. In addition, we investigated whether relational representations supported by hippocampus can be accessed quickly enough to be used in the course of online language processing.

Does MTL Contribute to Creativity?

Initial studies of hippocampal amnesia described complex cognitive functions, such as intelligence and decision making, as intact subsequent to medial temporal lobe (MTL) damage, causing early theoretical and experimental work to dismiss the notion that MTL contributes to more complex functions like creativity. Now evidence exists that contributions of MTL extend to several cognitive domains, beyond its isolated role in long-term memory (LTM). The functional contribution of individual MTL sub-regions, though, is disputed.

Hardly, any consideration has been given to whether contributions from MTL support the neural basis of creativity. A sophisticated view of MTL function characterizes the ability of hippocampus to bind arbitrary relations and permit flexible expression of information. Flexible expression of information permits interaction with neocortical storage sites to support integration and use of representations under a variety of circumstances (Cohen & Eichenbaum, 1993; Eichenbaum & Cohen, 2001).

Relational memory theory does not isolate hippocampal function as limited to long-term or episodic memory. Instead, it resonates with recent findings demonstrating the contribution of MTL to tasks that require relational processing - the ability to bind arbitrary relations and permit flexible expression of information, as well as findings demonstrating the contributions are fundamentally the same in nature, even if the task takes place on the time scale of short-term memory.

Evidence is growing that suggests: MTL contributes to relational tasks that (1) take place on the time scale of short-term or working memory (Hannula et al., 2006; Olson et al., 2006; Warren et al., 2011), (2) involve imagination of future or past events (Addis, Wong, & Schacter, 2007; Hassabis, Kumaran, Vann, & Maguire, 2007), (3) involve creative use of language (Duff, Hengst, Tranel, & Cohen, 2009), and (4) involve reconstruction of visually presented displays (Watson et al., 2013).

These findings are consistent with views of relational memory theory. MTL is predicted to contribute to aspects of creativity: the degree to which the task involves relational processing -

i.e. the <u>flexible</u> processing of converging inputs from various association cortices (Cohen & Eichenbaum, 1993; Eichenbaum & Cohen, 2001).

Creativity, Hippocampus, and Flexible Expression

A precise definition of creativity is not generally agreed upon. Researchers, however, have characterized aspects of creative thinking, including (1) the ability to produce ideas or responses that are novel and appropriate (Flaherty, 2005; Sternberg & Lubart, 1999), (2) the rapid combination and recombination of mental representations to create new ideas (Bristol & Viskontas, 2006), (3) the ability to generate, manipulate, and recognize novel conceptual representations (Damasio, 2001), and (4) the use of cognitive flexibility (Dietrich, 2004).

Most cognitive neuroscientists theorize the neural basis of creativity involves important contributions from frontal lobes (Dietrich, 2004; Dietrich & Kanso, 2010; Heilman, Nadeau, & Beversdorf, 2003). Perhaps frontal lobes support creativity by utilizing strong connections with polymodal and supramodal regions of temporal and parietal lobes where concepts and knowledge are stored (Heilman et al., 2003)? Or, maybe particular prefrontal circuits are critical to creativity, like making novelty fully conscious, evaluating appropriateness, and implementing creative expression (Dietrich, 2004; Dietrich & Kanso, 2010)?

In Chapter 5, we characterize the neural basis of creativity, beyond frontal lobes, by examining whether MTL contributes to creativity. We tested participants with hippocampal amnesia on the nationally normed *Torrance Tests of Creative Thinking* (TTCT). If characteristic relational processing features, attributed to hippocampus, support processes involved in creativity (e.g., flexible manipulation of information, generation of novel ideas), then individuals with hippocampal amnesia should show deficits.

The Insight of Relational Memory Theory

The contributions of medial temporal lobe (MTL) to tasks that take place on the timescale of short-term memory (or less) provide evidence that no longer restrain MTL function to long-term memory (LTM), recognition memory, and episodic memory. Instead, researchers are wondering if MTL contributes to more cognitive functions than previously thought? (Cashdollar et al., 2011; Kumaran, 2008; Ranganath & Blumenfeld, 2005).

From the perspective of relational memory theory, MTL function does not need to be limited to its role in LTM. Rather, MTL is characterized by supporting different kinds of representations in distinct sub-regions. Hippocampus supports arbitrary, flexible relations while perirhinal cortex supports inflexible or fused item representations - Cohen & Eichenbaum, 1993; Eichenbaum & Cohen, 2001; Konkel, Warren, Duff, Tranel, & Cohen, 2008. This perspective inspires questions about the contribution of MTL during tasks that involve relational processing on the timescale of short-term memory, including tasks of perception, language, and creativity.

The contribution of MTL to domains beyond LTM is an important unanswered question. *Does MTL contribute to aspects of cognition, including perception, language and creativity, which take place on the timescale of short-term memory?* This question motivates the following set of experiments.

Relational memory theory proposes that perirhinal cortex supports binding of inflexible relations - i.e. **fused**, unitized, or configural representations (Cohen & Eichenbaum, 1993;

Cohen, Poldrack, Eichenbaum, 1997). In Chapter 3, we investigate whether perirhinal cortex supports **fused** binding of complex object representations, using a novel approach - i.e. functional magnetic resonance adaptation (Rubin et al., 2013).

Relational memory theory proposes hippocampus is necessary for <u>binding arbitrary relations</u> and permitting their flexible expression. Hippocampus supports information about co-occurrence of people, places, and objects, along with the spatial, temporal and interactional relations among them (Eichenbaum & Cohen, 2001). In Chapter 4, we investigate whether participants with hippocampal amnesia can form and use common ground, in terms of their ability to relate <u>arbitrary</u> pieces of information by monitoring eye-movements (Rubin et al., 2011).

Relational memory theory proposes hippocampus is necessary for <u>permitting flexible expression</u> of information. Hippocampus provides a <u>flexible</u> database for creating, updating, and juxtaposing, existing and novel mental representations (Cohen & Eichenbaum, 1993; Eichenbaum & Cohen, 2001). In Chapter 5, we ask whether hippocampus contributes to the <u>flexible</u> use of information, as revealed by performance of participants with hippocampal amnesia on verbal and figural tests of creativity - i.e. the Torrance Tests of Creative Thinking (Duff et al., 2013).

The characterization of MTL function provided by relational memory theory (Cohen & Eichenbaum, 1993; Eichenbaum & Cohen, 2001) is compared with alternative theories. In the domain of perception, relational memory theory and ideas of Bussey and colleagues are discussed. In the domain of language, relational memory theory and ideas of MacKay and colleagues, Ullman and colleagues, and Duff and colleagues are discussed. Finally, in the domain of creativity, relational memory theory and ideas of Heilman and colleagues, Dietrich and colleagues, and Duff and colleagues are discussed. Notably, relational memory theory offers a parsimonious, domain invariant account of MTL function.

CHAPTER 3: USING FMR-ADAPTATION TO TRACK COMPLEX OBJECT REPRESENTATIONS IN PERIRHINAL CORTEX[1]

Abstract

Brain regions in medial temporal lobe have seen a shift in emphasis in their role in long-term declarative memory to an appreciation of their role in cognitive domains beyond declarative memory, such as implicit memory, working memory, and perception. Recent theoretical accounts emphasize the function of perirhinal cortex in terms of its role in the ventral visual stream. Here, we used functional magnetic resonance adaptation (fMRa) to show that brain structures in the visual processing stream can bind item features prior to the involvement of hippocampal binding mechanisms. Evidence for perceptual binding was assessed by comparing BOLD (blood-oxygen-level-dependent) responses between fused objects and variants of the same object as different, non-fused forms (e.g., physically separate objects). Adaptation of the neural response to fused, but not non-fused, objects was in left fusiform cortex and left perirhinal cortex, indicating the involvement of these regions in the perceptual binding of item representations.

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[1] This chapter is accepted for publication in Cognitive Neuroscience and is referred to later in this document as "Rubin, Chesney, Cohen & Gonsalves, 2013". Rubin, R. D., Chesney, S., Cohen, N. J., & Gonsalves, B. D. (2013). Using fmr-adaptation to track complex object representations in perirhinal cortex. *Cognitive Neuroscience*. doi:10.1080/17588928.2013.787056

Introduction

There is a wealth of evidence in support of the idea that declarative memory depends on the integrity of structures in medial temporal lobe (MTL), in particular hippocampus. Recent research has focused on a theoretical debate about the possibility of different structures within MTL subserving different kinds of declarative memory. Specifically, there is growing evidence that while hippocampus is critical for relational or associative memory, the adjacent perirhinal cortex may be able to support memory for individual items (Brown & Aggleton, 2001; Cohen & Eichenbaum, 1993; Davachi, Mitchell, & Wagner, 2003; Rugg & Yonelinas, 2003). While earlier work focused on defining functions of hippocampus and adjacent MTL cortices in terms of putative cognitive processes such as recollection and familiarity, more recent work has focused on understanding the nature of representations supported by these distinct regions. Conceptually, the main difference between item memory and relational memory is that item memory consists of a configural or inflexible representation of an item in isolation, whereas relational memory flexibly represents items, along with other elements of an experience, including the spatial and temporal context (Cohen & Eichenbaum, 1993).

One effect of this focus on representations supported by MTL regions has been a shift in emphasis on the role of these regions in long-term declarative memory, to an appreciation of their role in cognitive domains beyond declarative memory, such as implicit memory (Hannula & Greene, 2012), working memory (Ryan & Cohen, 2004) and perception (Lee et al., 2005). Several recent theoretical accounts (Murray, Bussey, & Saksida, 2007; Saksida & Bussey, 2010) have emphasized the function of perirhinal cortex in terms of its role in the ventral visual stream, with a corresponding emphasis on a role for perirhinal cortex in perception rather than strictly memory. Such accounts emphasize that perirhinal cortex is situated at the top of a hierarchically organized system, in which representations of visual objects are built from simple features combined into more and more complex conjunctions as one moves from posterior to anterior in the ventral visual stream (Desimone & Ungerleider, 1989). Under such a view, perirhinal cortex participates in both perception and memory, by virtue of its role in forming representations of complex objects (Saksida & Bussey, 2010). Much of this work is based on lesion studies in non-human animals, though recent human lesion and neuroimaging studies have converged on a role for perirhinal cortex in the representation of complex objects. On the other hand, much of the research investigating the role of perirhinal cortex in item memory has utilized verbal or verbalizable visual stimuli, and indeed neuroimaging work has suggested a role for perirhinal cortex in conceptual implicit memory (Voss, Hauner, & Paller, 2009; Wang, Lazzara, Ranganath, Knight, & Yonelinas, 2010).

The current study uses fMR-adaptation (fMRa) to index the sensitivity of brain regions to complex object representations, taking advantage of the phenomenon of repetition suppression, which is a general property of neurons at the single-cell and population levels in the ventral visual stream (Desimone, 1996; Grill-Spector, Henson, & Martin, 2006). The basic logic of fMRa is to record the combined hemodynamic response to a train of stimuli, with the idea that if the same stimulus is repeated, each subsequent response will show “adaptation”, and be smaller than the previous response in regions that represent that property of the stimulus. The combined hemodynamic response to such repetition is then compared to conditions in which the stimuli or some aspect of the stimuli change across repetitions. This logic can be used to probe the nature of representations in cortical regions by manipulating some property of the stimulus on the last repetition and observing which regions recover from adaptation. Those regions that recover from adaptation are sensitive to changes in that property, while those regions which do not recover from adaptation are insensitive to that property, suggesting that they do not code that kind of information (Grill-Spector & Malach, 2001).

In this experiment, we manipulated the specific combination of visual forms that composed an object to bias the perception of a set of abstract features as either a single coherent object or as two separate objects. To encourage the perception of features as a single object, two visual forms were "fused" and moved together across the screen; while to encourage perception of features as two separate objects, the visual forms were non-overlapping and moved separately across the screen (see examples in Figures 3.1a and 3.1d, respectively). The critical comparison was between the condition in which the same fused object was presented across the duration of the trial (i.e. Fused item condition) to the condition in which a non-fused variant of two visual forms was presented immediately followed by a fused variant of the same visual forms (i.e. Paired item condition). In this way, the final stimulus is equivalent across conditions, what differs is the viewing history. Differences in activation between these conditions, revealed by *adaptation* or *recovery from adaptation*, would indicate which brain regions were sensitive to the fused vs. non-fused viewing history of the visual forms.

In early visual areas, we expected there to be little difference between the conditions because there is little difference between the conditions in terms of the properties to which early visual regions are sensitive, e.g., color, general shape, size, motion. In more anterior visual regions, especially perirhinal cortex, however, we expected differences between the conditions to emerge depending on whether the visual forms are fused in the movie portion of the trial. In the Fused item condition, the visual forms are presented as the same fused object in both the movie and subsequent static image; therefore we expected *adaptation* of the neural response in item processing areas that are sensitive to coherent complex visual objects. In the Size-Changing item condition, we expected a similar pattern of *adaptation*; though the size of the fused object is changing during the movie, the specific combination of visual forms does not change throughout the trial. Contrastingly, in the Novel item condition, the visual forms that compose the object in the movie are completely different to the visual forms that compose the object in the static image; therefore we expected *recovery from adaptation* of the neural response in item processing areas that are sensitive to the specific combination of features that compose an object. In the Paired item condition, we expected a similar pattern of *recovery from adaptation*. Even though there is overlap in the features of the visual forms, the specific combination of the visual forms change in that they appear separate during the movie and then fused during the static image. Such results would inform theories about the nature of complex object representations supported by perirhinal cortex, without requiring the relational binding mechanisms of hippocampus, which would be expected to be necessary for storing the link between visual forms that are spatially discontiguous.

Method

Participants

Participants were recruited through local advertisements in the University of Illinois community. Prior to enrollment in the study, participants were screened for contraindications to MRI examination. After an explanation of the study was given, informed written consent was obtained from all participants prior to initiation of the study. All procedures used were approved by the Institutional Review Board of the University of Illinois at Urbana-Champaign.

The study included 14 right-handed, native English-speaking adults age 18-28 (*Mean* = 21.5; 8 females). Apart from the 14 participants included in the study, 4 additional participants were excluded from analysis due to excessive movement artifacts in their fMRI data. All participants were financially compensated for their involvement in the study.

Stimuli and Design

The stimuli were computer rendered novel objects comprised of various combinations of separate visual forms (for examples see Figure 3.1). Individual study trials consisted of a 4-second movie showing the object(s) moving across the screen, a half-second fixation, and then a 1.5 second display of a static object. Study trials were from one of four conditions: Fused item, Size-Changing item, Novel item, and Paired item. The name of the condition describes the different kind of item(s) in the movie, as all trials ended with the presentation of a static object. In the Fused item condition, two visual forms were slightly overlapping, and the fused object translated across the screen as a single object followed by the presentation of the static version of the same fused object. In the Size-Changing item condition, a fused object expanded and contracted on the screen (size transformation), followed by a static version of the same fused object. This condition provided a control for movement across the screen, and thus across the visual field. In the Novel item condition, a fused object translated across the screen (as in the Fused item condition), but was followed by a static version of a completely different fused object. In the Paired item condition, two visual forms were non-overlapping and translated separately across the screen, followed by the presentation of a static version of the same two visual forms combined into a fused object. Each Study block was followed by a Test block in which individual test trials consisted of a 4s presentation of a static object. Some of the static objects were the same static objects seen in the previous study block, while others were completely novel objects.

Procedure

The experiment consisted of four study-test blocks inside the scanner. Trials were intermixed in a pseudorandom order including null fixation events to facilitate deconvolution of the hemodynamic response to individual conditions. Before each study block, participants were instructed to study the following displays and pay attention to the movement. They were also informed that there would be a subsequent memory test. Each study block consisted of 28 trials as described above (7 from each condition). The study block was immediately followed by instructions for the test block. Participants were told they would make judgments about which displays they had previously seen. Participants made combined recognition confidence judgments (1 = “confident new”, 2 = “unsure new”, 3 = “unsure old”, 4 = confident “old”). Each test block (N=42) consisted of trials containing a static object, 28 were previously seen and 14 were new.

fMRI Data Acquisition

Imaging was performed using a 3-Tesla Siemens Magnetom Allegra MRI scanner (Siemens Medical Solutions, Erlangen, Germany) at the University of Illinois Biomedical Imaging Center. Participants viewed visual stimuli on a back-projection screen using an angled mirror mounted on the head coil.

After acquisition of a T2 localizer scan, four functional gradient echo-planar imaging (EPI) runs were collected, each 11:16 minutes (TR = 2000ms, TE = 25ms, 38 interleaved oblique coronal slices, 0.42mm interslice-gap, $3.4 \times 3.4 \times 3$ mm^3 voxels, flip angle = 80º, field of view = 220 mm, 336 volumes per run). Oblique coronal slice acquisition perpendicular to the main axis of the hippocampus was used to minimize susceptibility artifacts in anterior temporal lobe regions during fMRI data acquisition. Slices were positioned to ensure complete coverage of the occipital lobe, at the expense of excluding the frontal poles for participants for whom whole-brain coverage was not possible. Following the four functional runs, high-resolution T1 MPRAGE anatomical images were acquired. Following the four functional runs, a high-resolution T1 MPRAGE anatomical image was acquired (scan time = 6:58min, TR = 2000ms, TE = 2.22ms, 112 ascending sagittal slices, 0.75mm slice-gap, $1.1 \times 1.1 \times 1.5$mm^3 voxels, flip angle = 8º, field of view = 220 mm).

fMRI Data Analysis

The data were preprocessed using SPM5 (Wellcome Department of Cognitive Neurology, London, UK; http://www.fil.ion.ucl.ac.uk/spm/software/spm5/). For each participant, functional images were adjusted for interleaved slice acquisition and were then subjected to affine motion correction. Resulting images were visually inspected for quality of motion correction. Functional volumes were then normalized to the SPM echo-planar imaging template and resampled to $3 \times 3 \times 3$ mm^3 voxels. T2-weighted localizer images were then coregistered to the mean EPI volume across runs, and high-resolution T1 MPRAGE images were coregistered to T2-weighted images. Finally, functional images were smoothed with an 8mm full-width at half maximum isotropic Gaussian kernel to reduce noise.

It is important to note that a study block “event” in this event related fMRI design consisted of a compound response to the object movie and the subsequent static object. In this sense, the design is akin to adaptation paradigms that consider the combined BOLD response to trains of stimuli. Functional data were modeled using the Finite Impulse Response (FIR) model in SPM5 because (1) we expected an extended hemodynamic response to our compound events and (2) the FIR model does not make assumptions about the shape of the hemodynamic response function. Direct contrasts between conditions were carried out using t-contrasts at the subject level. Subsequent to individual subject analyses, random-effect group analyses were performed for each contrast using one-sample t-tests, comparing the value of the contrast images against zero.

In addition to these voxel-based random-effects analyses, targeted ROI analyses were performed to examine the activity in functionally-defined brain regions using the MARSBAR toolbox (Brett, Anton, Valabregue, & Poline, 2002). Functional ROIs were used to characterize the responses of regions that were predicted to be involved in item processing. ROIs were defined in an unbiased manner by contrasting all study trials with fixation trials to identify regions generally involved in processing the stimuli. 8mm spheres were constructed around peak activations in ROIs that were sufficiently large - otherwise the entire functional activation was used. Then peak BOLD responses were calculated for each condition for each ROI and were subjected to repeated measures ANOVA *F*-tests to compare activity across conditions.

Results

Behavioral Test Block Results

The mean percent correct for the recognition memory data was calculated (Fused item = 76%, Size-Changing item = 73%, Novel item = 60%, Paired item = 75%, and New item = 81%)

and a one-way repeated measures ANOVA of condition with five levels was performed. An omnibus F-test showed significant differences between conditions ($F_{4, 52} = 7.88$, $p < .005$[2]). Planned pairwise comparisons between Fused item vs. Novel item, Size-Changing item vs. Novel item, Paired item vs. Novel item, and New item vs. Novel item were all significant ($4.38 <|t_{13}| < 6.14$, all ps $\leq .001$). The mean confidence ratings for the recognition memory data were also calculated (Fused item = 3.28, Size-Changing item = 3.20, Novel item = 2.83, Paired item = 3.21, and New item = 1.83) and a one-way repeated measures ANOVA of condition with five levels was performed. An omnibus F-test showed significant differences between conditions ($F_{4, 52} = 69.07$, $p < .001$). Planned pairwise comparisons between Fused item vs. Novel item, Novel item vs. New item, Paired item vs. Novel item, Size-Changing vs. Novel item, Fused item vs. New item, Paired item vs. New item, and Size-Changing vs. New item were all significant ($5.84 <|t_{13}| < 10.45$, all ps $< .001$).

fMRI Study Block Results

To assess differences in neural activity across the four conditions a region-of-interest (ROI) analysis was performed in targeted brain regions that were active across all conditions to compare relative amounts of peak activation. Differences between regions in varying degrees of peak activation were predicted depending on whether *adaptation* or *recovery of adaptation* (of the neural response) to the static image was expected during the trial. All regions that showed significant activation to the objects in the four conditions compared to fixation ([Fused item, Size-Changing item, Paired item, Novel item] > fixation, p< .005, five contiguous voxels) were calculated. From this general set of regions, we selected three a priori ROIs based on regions

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[2] Hereafter, where violations of sphericity occurred, Greenhouse-Geisser corrected p-values are reported; for clarity, unadjusted df are reported.

implicated in item processing, including areas in *visual cortex*, *fusiform cortex* and *perirhinal cortex* (Davachi, 2006; Gonsalves, Kahn, Curran, Norman, & Wagner, 2005; Tanaka, 1997). Each ROI was an 8mm sphere around the peak of the functional activation cluster for all trials greater than fixation ($p < .001$, five contiguous voxels), except in perirhinal cortex in which the entire functional activation was used. Coordinates indicate the center of mass for each cluster.

Region-of-Interest Analysis

First, we focused on the critical comparison between the Fused item and Paired item conditions, where there was the largest overlap between the individual features of either a single visual form (i.e. Fused item) or non-fused visual forms (i.e. Paired item). As our predictions suggested, there were no differences between these two conditions in early bilateral visual areas: Left middle occipital gyrus (MNI coordinates: -36, -87, 9) and right middle occipital gyrus (MNI coordinates: 39, -84, 6), $t = .89$, $p > .05$[3] and $t = 1.24$, $p > .05$, respectively. Differences between the Fused item and Paired item condition, however, emerged as early as left fusiform cortex (MNI coordinates: -33, -60, -15), $t = -2.91$, $p < .05$, as well as left perirhinal cortex (MNI coordinates: -24, -6, -39), $t = -1.87$, $p < .05$ (see Figure 3.2). In these regions, the Paired item condition showed recovery from adaptation relative to the Fused item condition.

ROI results from the Size-Changing item and Novel item conditions further support the adaptation results from the critical comparisons between the Fused item and Paired item conditions. There was a main effect in left fusiform cortex ($F_{3,39} = 5.70$, $p < .05$) and all planned comparisons were significant between conditions in which adaptation was expected versus conditions in which recovery was expected: Size-Changing item vs. Paired item ($t = -3.45$,

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[3] One-tailed thresholds were used for the remaining contrasts given that fMRI adaptation lends itself to clearly directional predictions.

$p < .05$), Size-Changing item vs. Novel item ($t = -2.18$, $p < .05$), Fused item vs. Novel item ($t = -4.26$, $p < .05$). Furthermore, our predictions were supported by finding no differences between the two conditions in which adaptation was predicted: Size-Changing item vs. Fused item ($t = 0.72$, $p > .05$), as well as no differences between the two conditions in which recovery from adaptation was predicted: Novel item vs. Paired item ($t = 0.71$, $p > .05$). In left perirhinal cortex a main effect failed to reach significance ($F_{3,39} = 0.93$, $p > .05$); although as mentioned previously, the critical comparison was significant between the Fused item vs. Paired item condition, $t = -1.87$, $p < .05$.

Discussion

The results of this study suggest that fMR-adaptation can be used to show differences in item processing throughout the visual system and early MTL regions. In early visual areas, the BOLD response elicited by the Fused item and Paired item conditions was similar. This suggests that early bilateral visual areas processed low-level object features (e.g., general object shape, color), which indeed were designed to be similar between the two critical conditions. In late visual and early MTL regions, the BOLD response elicited by the Fused item and Paired item conditions was different, suggesting these regions represented specific combinations of item features as a fused object, prior to hippocampal processing. Specifically, BOLD activity in fusiform and perirhinal cortex showed recovery from adaptation in the Paired item condition when the two non-fused visual forms were presented and then immediately followed by a fused variant of the same two visual forms. This suggests that these regions are sensitive to specific high-level object features (e.g., object identity, specific feature combinations of an item). In contrast, BOLD activity showed adaptation in these same regions in the Fused item condition when the same fused object was shown throughout the trial. These results are consistent with the notion that fusiform and perirhinal cortex play a role in representing complex combinations of visual features that comprise objects.

One implication of this result is that perirhinal cortex, in this respect, behaves like other regions in the ventral visual stream. It forms object representations taking into account information such as spatial contiguity and does not obligatorily create fused object representations out of features present in the visual world that are spatially discontiguous, which is consistent with accounts that emphasize the role of perirhinal cortex in representation of complex objects (Bussey, Saksida, & Murray, 2002, 2005). Other work in primates, however, has provided evidence for the role of perirhinal cortex in representation of pairs of objects (Fujimichi et al., 2010; Miyashita, 1988; Sakai & Miyashita, 1991). One difference between that work and the present study is that in the work of Miyashita and colleagues, pair coding neurons in perirhinal cortex develop response selectivity to pairs of objects over a relatively large number of repeated encounters with the same object pairs. Thus, perirhinal cortex may come to represent object pairs after repeated exposure to those pairs, rather than during a single trial as in our present experiment.

Questions also remain about the role of perirhinal cortex in the online creation of fused items from initially disparate elements, especially under task instructions to mentally fuse the elements into a single item. Results from the literature on “unitization” support such a role for perirhinal cortex in conceptual unitization in humans, though most of these studies have relied on verbal stimuli (Haskins, Yonelinas, Quamme, & Ranganath, 2008; though see Staresina & Davachi, 2010). Other studies of unitization have used either amnesic patients with hippocampal damage or event-related potentials and thus can provide only indirect evidence concerning the specific role of perirhinal cortex in unitization (Bader, Mecklinger, Hoppstädter, & Meyer, 2010; Diana, Van den Boom, Yonelinas, & Ranganath, 2011; Opitz & Cornell, 2006; Pilgrim, Murray, & Donaldso, 2012; Quamme, Yonelinas, & Norman, 2007; Rhodes & Donaldson, 2007, 2008). Further research is needed to establish the role of perirhinal cortex in unitization in which more purely visual forms need to be fused online to form novel visual object representations, as well as to directly contrast the role of perirhinal cortex in perceptual vs. conceptual unitization.

An intriguing possibility is that the adaptation technique employed in the current study could be used as a marker of online unitization in situations that require the volitional combination of spatially discontiguous items - more akin to the studies cited above that address the role of unitization in associative memory. Such a neural marker of unitization could potentially be assessed for its relationship to subsequent memory performance, in that it may be possible to predict subsequent memory performance based on the amount of adaptation that occurred during unitization. The prediction in this case would be that the more successfully the items were unitized during study, as indexed by neural adaptation, the more likely the unitized version will be recognized during subsequent memory testing on the basis of familiarity - without the need for relational memory representations supported by the hippocampus. If such a relationship is found, this method may be considered a powerful tool for assessing the nature of representations implemented in cortical regions surrounding the hippocampus, and thus provide valuable data informing our understanding of the roles of these regions in long term memory and in other cognitive domains.

Figures

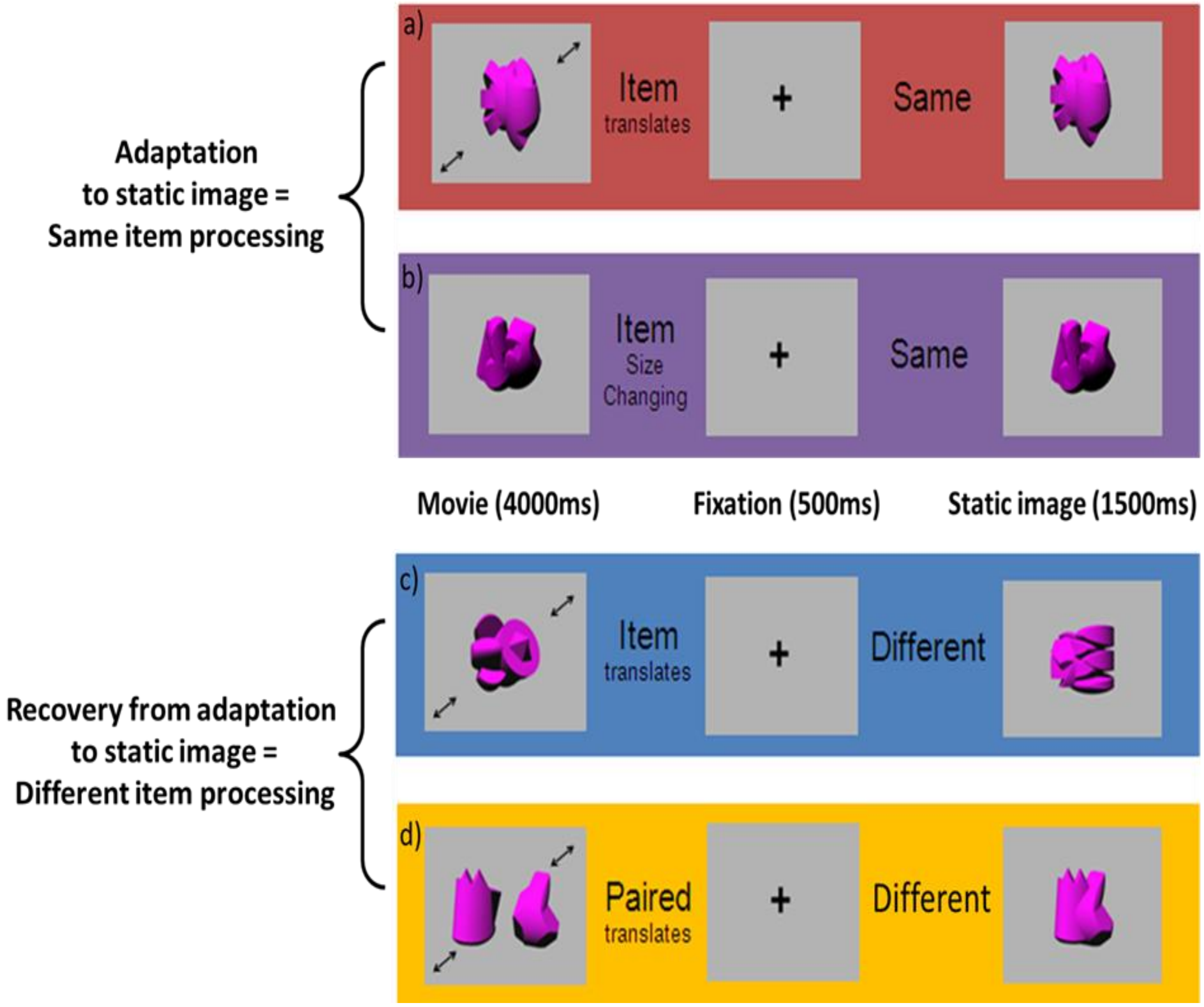

Figure 3.1. Experimental stimuli and trial structure. a) Fused item condition (red box), b) Size-Changing item condition (purple box), c) Novel item condition (blue box), d) Paired item condition (yellow box). The critical comparison is between the Fused item condition and Paired item condition, in which the final stimulus in both conditions is equivalent, however, the viewing history differs. It is essential to the design that in both the Fused item and Paired item conditions the visual forms are similar across the trial, but only in the Paired item condition are the visual forms physically separated. Differences in activation between these conditions indicate which brain regions are sensitive to the fused vs. non-fused viewing history of the visual forms (and not the perceptual similarity of the forms).

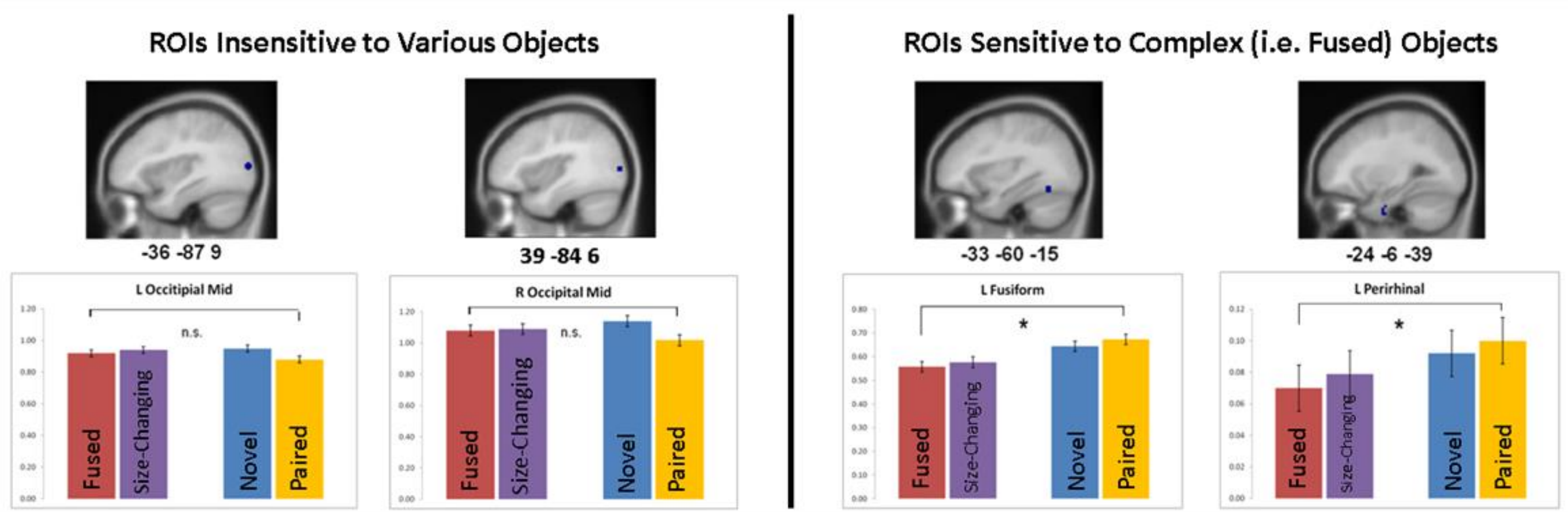

Figure 3.2. Selected item processing ROIs (same color coding as Figure 3.1). ROIs Insensitive to Various Objects (left panel): Left middle occipital gyrus and right middle occipital gyrus. ROIs Sensitive to Complex (i.e. Fused) Objects (right panel): Left fusiform and left perirhinal. Highlighted regions indicate 8mm sphere around the peak of the functional activation cluster for all trials greater than fixation ($p < 0.001$, five contiguous voxels), except left perirhinal in which the entire functional activation cluster was used. Coordinates indicate the center of mass for each cluster. Bar graphs depict average activity of the highlighted region for the peak timepoint of the modeled FIR timecourse. Error bars represent within-subjects SE. *p<.05.

CHAPTER 4: HOW DO I REMEMBER THAT I KNOW YOU KNOW THAT I KNOW?[4]

Abstract

Communication is aided greatly when speakers and listeners take advantage of mutually shared knowledge (i.e., common ground). How such information is represented in memory is not well known. Using a neuropsychological-psycholinguistic approach to real-time language understanding, we investigated the ability to form and use common ground during conversation in memory-impaired participants with hippocampal amnesia. Analyses of amnesics' eye fixations as they interpreted their partner's utterances about a set of objects demonstrated successful use of common ground when the amnesics had immediate access to common-ground information, but dramatic failures when they did not. These findings indicate a clear role for declarative memory in maintenance of common-ground representations. Even when amnesics were successful, however, the eye movement record revealed subtle deficits in resolving potential ambiguity among competing intended referents; this finding suggests that declarative memory may be critical to more basic aspects of the online resolution of linguistic ambiguity.

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[4] This chapter appears in its entirety in Psychological Science and is referred to later in this document as "Rubin, Brown-Schmidt, Duff, Tranel & Cohen, 2011". Rubin, R. D., Brown-Schmidt, S., Duff, M. C., Tranel, D., & Cohen, N. J. (2011). How do I remember that I know you know that I know?. *Psychological Science, 22*(12), 1574-1582

Introduction

During conversation, individuals build and maintain representations of common ground, the information they jointly share with their conversational partner (Clark & Marshall, 1978, 1981; Stalnaker, 1978). Common ground is thought to be a central, if not the most central, component of discourse understanding (Clark, 1992), as it shapes both what partners talk about and how they talk about it (Clark & Wilkes-Gibbs, 1986; Horton & Gerrig, 2005a). Examples are seen in the successful use of one of the most frequent linguistic forms, definite reference (e.g., “that cake,” “our dog”), which requires that the speaker and addressee jointly believe that the referent is identifiable in their common ground with respect to multiple candidate objects to which the speaker might refer (Clark & Marshall, 1978, 1981).

In successful conversations, partners jointly establish shared names for the objects, places, and things they talk about. These names confer clear communicative advantages, but only for partners who share the names in common (Schober & Clark, 1989; Wilkes-Gibbs & Clark, 1992). It is critical to note that representations of what information is shared and what information is private can facilitate the moment-by-moment decisions that listeners make as they understand language in practice (Brown-Schmidt, Gunlogson, & Tanenhaus, 2008; Hanna, Tanenhaus, & Trueswell, 2003; Metzing & Brennan, 2003; but see Barr, 2008, for an alternative view on the precise timing of these effects). That is, common-ground information can help to resolve potential ambiguity in online linguistic processing. Note that such a role is possible only if such information is stored in memory in a form that can be accessed within the time frame of online processing. The dominant view of common-ground representations is that when individuals encode information about events, they tag those memories with information about who was there and what each person’s role was in that event (Clark & Marshall, 1978, 1981). Such putative common-ground representations include information about things that were jointly experienced by the partners, either because those things were visually co-present, linguistically mentioned, or culturally shared. For example, if Eleanor and Otto go to a movie together, Eleanor’s memory of the event includes the information that it was Otto who saw the movie with her. This example of common ground emphasizes declarative memory and the relational representations it supports of the elements of experience - including information about the co-occurrences of people, places, and objects along with the spatial, temporal, and interactional relations among them - as part of the record of one’s experience over time (Cohen & Eichenbaum, 1993; Eichenbaum & Cohen, 2001).

Declarative, or relational, representation of common ground seems rich enough to support the ability to remember complex representations, such as that I know you know that I know, and to permit the speaker to take advantage of this information. But an important question, one that we addressed in the study reported here, remains: Can such representations be accessed quickly enough to be used in the course of online processing in language interactions? The sorts of relational representations ascribed to declarative memory are often thought to be essential in deliberative, consciously mediated retrieval, rather than in the very rapid and possibly implicit retrieval needed for online processing during language interactions.

There are alternative ideas about the representational basis for common ground that do not require declarative memory. One view suggests that interlocutors align their mental models via priming at many levels of linguistic representation (Pickering & Garrod, 2004). Alignment results in implicit common ground; explicit modeling of other peoples’ mental states occurs only when necessary. Horton and Gerrig (2005a, 2005b) suggested that low-level, automatic, cue-based associations between partners may serve as the basis for much common ground. Although they do not specify the kind of memory that would support such associations, they contrast it with the “reference diary” kind of explicit representation advocated by Clark and his colleagues (e.g., Clark & Marshall, 1978). An advantage of the view proposed by Horton and Gerrig is that it offers a reconciliation of findings of rapid use of common ground during online understanding (Hanna et al., 2003) with assertions that accessing common-ground representations would be too resource intensive to routinely guide language processing (Keysar, Barr, Balin, & Paek, 1998). In this view, as with the priming-based proposal, explicit calculations of common ground are not always necessary for common-ground-based inferences.

In the study reported here, we examined the representational basis of common ground by testing amnesic patients with selective impairment of declarative memory. In the only prior study of common ground in patients with amnesia (Duff, Hengst, Tranel, & Cohen, 2006), we demonstrated that amnesic participants can establish shared names for novel shapes with a communication partner across multiple trials, despite their profound memory impairments. This finding indicates that at least one kind of common ground is used by amnesics (but see Wu & Keysar, 2007, who speculated that the amnesic participants may have succeeded on the basis of their private knowledge alone).

In the present study, we employed eye movement measures to test the degree to which declarative memory is necessary in establishing common ground with a partner and in using common-ground information to guide online language understanding. Little is known about the real-time language-processing abilities of individuals with amnesia, as most previous work has used off-line measures or explicit judgments (e.g., Duff, Hengst, Tranel, & Cohen, 2007; MacKay, Burke, & Stewart, 1998). Previous studies have shown that neurologically intact listeners rapidly integrate visual and linguistic information, fixating objects whose names have the same initial sounds of a target word within 200 ms of word onset (Allopenna, Magnuson, & Tanenhaus, 1998) and ruling out privileged-ground competing objects within approximately 400 ms (Hanna et al., 2003; Heller, Grodner, & Tanenhaus, 2008). However, no study has rigorously examined the time course with which participants with hippocampal amnesia interpret spoken words in real-time. By tracking participants' eye movements as they process language in real-time, we provided novel insights into if and how declarative memory might contribute to online processing and, more specifically, to the resolution of ambiguity in a naturalistic conversational setting.

In our study, each amnesic (or healthy matched comparison) participant completed a task with an experimenter in which they jointly viewed scenes with objects. Some of these objects were in common ground, and some of them were in the amnesic participant's privileged ground. Participants were asked to look at some target object. For example, the experimenter asked the amnesic participant to "Look at the cactus" in scenes containing two cacti. In some conditions, only one of the two cacti was in common ground. Thus if the amnesic participant represented common ground, he or she could use this information to resolve the ambiguity (Figure 4.1a). By monitoring the eye movements made by amnesic participants as they interpreted the experimenter's instructions, specifically by measuring the distribution of viewing to the various potential target objects and the changes in viewing over time, we were able to determine if and when amnesic participants accessed common-ground representations and then used them to facilitate online language understanding.

If the use of common ground to resolve linguistic ambiguity requires access to declarative memory representations (Clark & Marshall, 1978), amnesic participants should show deficits in all of these tasks and dramatic failures when there is no external memory cue. Alternatively, if nondeclarative representations of common ground (Horton & Gerrig, 2005a, 2005b; Pickering & Garrod, 2004) can be used to resolve ambiguity, we would expect amnesic participants to perform as well as healthy participants.

Method

Participants

Five amnesic participants (1 female, 4 male) with bilateral hippocampal damage due to anoxia (n = 3) or herpes simplex encephalitis (n = 2) participated. The amnesic participants had severe and selective declarative memory impairments yet generally preserved intelligence and cognition (e.g., language skills). Table 4.1 summarizes the demographic and neuropsychological characteristics of the amnesic participants. Five healthy participants were matched pairwise to the 5 amnesic participants on age, handedness, education, and sex.

Stimuli and Design

The experimenter and participant were seated facing each other and each viewed a separate three-dimensional rendering of a 3 × 3 cubbyhole display with everyday objects on their respective computer screens (Figure 4.1). These screens were placed back to back to give participants the illusion that they and the experimenter were viewing the same display from opposite sides. The participant’s display contained open cubbyholes (through which the green background behind the display could be seen) in the top row, closed cubbyholes in the middle row, and partially closed cubbyholes (i.e., closed at the back but open at the front) in the bottom row. Objects shared between the participant and the experimenter appeared in the top row, and privileged objects (those visible only to the participant) appeared in the bottom row. A green poster board was placed on the wall behind the experimenter to encourage the perception that the open (green) cubbyholes held shared objects. The experimenter's display contained open cubbyholes with shared objects in the top row, partially closed cubbyholes with the experimenter's privileged objects in the middle row, and closed cubbyholes in the bottom row. A fixation cross was presented in the middle cubbyhole of the two displays throughout the duration of each trial.

The objects used in the display were 174 colorized drawings of easily nameable objects from the Snodgrass and Vanderwart database (Snodgrass & Vanderwart, 1980; Rossion & Pourtois, 2004) and similar pictures. The participant's gaze was recorded at 250 Hz using an EyeLink 1000 portable remote eye tracker (SR Research, Kanata, Ontario, Canada). Headset microphones recorded the speech of both partners.

Procedure

We examined two types of common ground: common ground for information that was visually shared and common ground for information that was linguistically mentioned. Although both visual and linguistic information can be used to establish common ground, linguistic evidence may be weaker and more susceptible to memory decay over time (Clark & Marshall, 1978).

To test the use of visual common ground, we compared online interpretation in two conditions, one in which the referent of the critical object named by the experimenter was ambiguous, and one in which visual common ground resolved the ambiguity. On 18 trials in the visually ambiguous condition, the experimenter first asked the participant to “Look at the cross” in the center of the screen, and then told participants to look at a specific object (e.g., “Look at the cactus”). It is crucial to note that in this condition there were two identical objects in the common ground between the experimenter and participant, making the experimenter’s instruction to look at a specific object ambiguous (Figure 4.1b). The 18 trials in the visually unambiguous condition followed the same format, except that although the target was visually shared, the competitor (i.e., a second object identical to the target object) was in the participant’s privileged ground (Figure 4.1a). If participants can use common ground to constrain online interpretation of the experimenter’s instructions, they should look significantly more often at the shared target in the unambiguous condition than in the ambiguous condition. On each of 36 filler trials, the experimenter instructed the participant to look at a visually shared object for which there was no corresponding competitor (e.g., in the display shown in Figure 4.1a, the experimenter would say “Look at the snake”).

To test the use of linguistic common ground, we created situations in which a privileged-ground object was introduced into the discourse by the participant and then subsequently mentioned immediately by the experimenter (no-delay condition) or after a delay (filled-delay condition; Figure 4.1b). The delay manipulation allowed us to examine whether linguistic common ground was maintained over time. On each trial, the experimenter first asked about a privileged object (e.g., “What’s in your bottom left cubby?”). The participant’s response (e.g., “An elephant”) would bring that visually privileged target object into linguistic common ground. Then, after no delay (on 18 trials) or a filled delay (on 18 trials), the experimenter asked participants to “Look at the cross” and then look at the linguistically mentioned privileged object (e.g., “Look at the elephant”). On the filled-delay trials, participants were instructed to form a short story about two of the shared objects. Example stories were provided by the experimenter if the participant was unable to produce a story on his or her own; participants' stories lasted approximately 40 s. During the filled delay, the display was left on the screen, and the participants tended to look at the shared objects mentioned in the story. Filler trials followed the same format, except that the experimenter ultimately asked the participant to look at a visually shared object (e.g., "Look at the zebra").

Results

Analyses were performed on eye movements following the onset of the critical word in the experimenter's final instruction (e.g., "cactus" in "Look at the cactus"). We report results of two types of analyses. First, we examined the time course of target identification in the visual and linguistic common-ground conditions. Gaze was analyzed in terms of target advantage, which is the average proportion of looks to the target minus the average proportion of looks to the competitor. Target-advantage scores were analyzed across eight 400 ms time epochs beginning 200 ms prior to the start of the critical word. The first epoch served as a baseline because of the time needed to program and launch a saccade (Hallett, 1986). Our second set of analyses focused on those conditions in which amnesic participants successfully interpreted the final instruction; these analyses examined participants' ability to rule out potential competitors during online comprehension. These analyses tested for evidence of unresolved competition by analyzing all competitor fixations following critical-word onset.

Identification of targets in visual common ground

Both amnesic and healthy participants rapidly used common ground to successfully interpret the critical instruction as asking about the visually shared referent and not the identical visually privileged object (Figure 4.2). An analysis of variance (ANOVA) with condition, epoch, and participant group as factors revealed a main effect of condition due to significantly higher target advantage when common ground ruled out the competitor in the visually unambiguous condition, $F_1(1, 8) = 288.26$, $p < .0001$; $F_2(1, 17) = 119.25$, $p < .0001$[5]. A main effect of epoch, $F_1(7, 56) = 16.29$, $p < .0001$; $F_2(7, 119) = 20.14$, $p < .0001$, reflected the increase in target fixations following critical-word onset. An epoch-by-condition interaction was significant, $F_1(7, 56) = 11.82$, $p < .0001$; $F_2(7, 119) = 23.66$, $p < .0001$, suggesting that the condition effect emerged over time. It is critical to note that planned one-tailed comparisons demonstrated that results in the healthy and amnesic groups did not differ across any of the eight epochs in either condition, *t*s < 1.97, *p*s > .05.

These results demonstrate that both healthy and amnesic participants distinguish between visually shared and private information as they interpret language online. When only one referent of the critical word was in common ground between the participant and the experimenter, and thus the domain of interpretation was restricted, participants directed attention toward the target and away from the competitor object. When two referents of the critical word were in common ground, and thus the domain of interpretation was not constrained, fixations to the target and to the competitor did not diverge.

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[5] Hereafter, when violations of sphericity occurred, we report Huynh-Feldt corrected p values; for clarity, unadjusted degrees of freedom are reported. The F_2 statistic is standard for linguistic analyses; it treats item as a random factor.

Identification of targets in linguistic common ground

Both healthy and amnesic participants successfully used linguistic common ground to resolve ambiguities in the experimenter's instructions. However, for the amnesic participants, this was true only in the no-delay condition, with severe deficits following a filled delay (Figure 4.3). An ANOVA with condition, epoch, and participant group as factors revealed main effects of both condition, $F_1(1, 8) = 38.60$, $p < .0001$; $F_2(1, 17) = 61.63$, $p < .0001$, and epoch, $F_1(7, 56) = 28.53$, $p < .0001$; $F_2(7, 119) = 75.97$, $p < .0001$. These main effects were qualified by an epoch-by-group interaction, $F_1(7, 56) = 4.24$, $p < .01$; $F_2(7, 119) = 12.18$, $p < .0001$, and a condition-by-epoch interaction, $F_1(7, 56) = 11.00$, $p < .0001$; $F_2(7, 119) = 15.05$, $p < .0001$. It is critical to note that a condition-by-epoch-by-group interaction, $F_1(7, 56) = 4.03$, $p < .05$; $F_2(7, 119) = 5.84$, $p < .0001$, indicated that the way in which the condition effect emerged over time differed between the two groups.

Planned one-tailed comparisons demonstrated that in the no-delay condition, results from the healthy and amnesic groups did not differ across any of the eight epochs, ts < 1.35, ps > .1. In the filled-delay condition, however, planned one-tailed comparisons demonstrated that the healthy participants outperformed the amnesic participants between Epochs 4 and 8 (1,000–3,000 ms), ts > 2.01, ps < .05. The lack of a difference between the groups prior to 1,000 ms may be due to a slight (but nonsignificant) preference for amnesic participants to fixate on the target prior to 1,000 ms.

These results suggest that amnesic participants retain representations of what information is in linguistic common ground only when there is no delay between when they introduce the privileged object into the discourse and the experimenter's instruction to look at it. Following a brief (~40 s) side conversation about another topic (e.g., the shared objects in common ground), the shared information is no longer available to the amnesic participants, and they are unable to determine which object is being referenced by the experimenter.

Fixations on competitor objects

Although amnesic participants successfully identified the target over the competitor in the visually unambiguous and linguistic no-delay conditions, further analyses examined the level of viewing of competitor objects, even when interpretation was successful. Planned one-tailed comparisons of fixations to competitor objects during the period between 200 ms and 3,000 ms following critical-word onset in the visually unambiguous condition demonstrated that amnesic participants made more fixations to the competitor object than did healthy participants, $t(8) = -1.92$, $p < .05$. In the linguistic no-delay condition, the results between groups did not differ ($p > .05$), although amnesic participants fixated on the competitor object at greater than chance levels ($p = .05$), and healthy participants did not ($p > .05$). The differences in results between the amnesic and healthy participants in these conditions were clearly related to the presence of the competitor, as fixations on the target object in the filler trials did not differ between the groups. Although amnesic participants fixated on the target more than on the competitor within the first second of critical-word onset, the lingering fixations to the competitor suggest that even when interpretation is successful and rapid, hippocampal amnesia may impair the very earliest moments of language understanding, and declarative memory may be critical.

Discussion

The results of this study demonstrate a clear role for declarative memory in the use of common ground during conversation; they also demonstrate that representations of what information is shared or private can guide real-time language understanding in the absence of declarative memory support. These findings have implications concerning the nature of common-ground representations, and they speak directly to conflicting theoretical views about the kind of memory required in the use of common ground. The findings also provide evidence of deficits in the resolution of competition between visually identical shared and privileged objects during online speech processing in individuals with hippocampal amnesia, offering new insights about the possible role of declarative memory in real-time language processing.

According to the classical view, conversational partners represent common-ground information in “reference diaries,” in which explicit memories of events are tagged with information about who jointly experienced that event (Clark & Marshall, 1978, 1981). According to this view, there is a clear role for declarative memory in representations of common ground. The fact that amnesic participants with severe impairments in declarative memory were unable to maintain representations of items in common ground across a brief (~40 s) filled delay is consistent with this view. Given the impairments in the use of common ground evident even with the brief delays used here, it is clear that the usual benefits conferred by common ground to speakers in real-life communication will be compromised significantly in these patients.

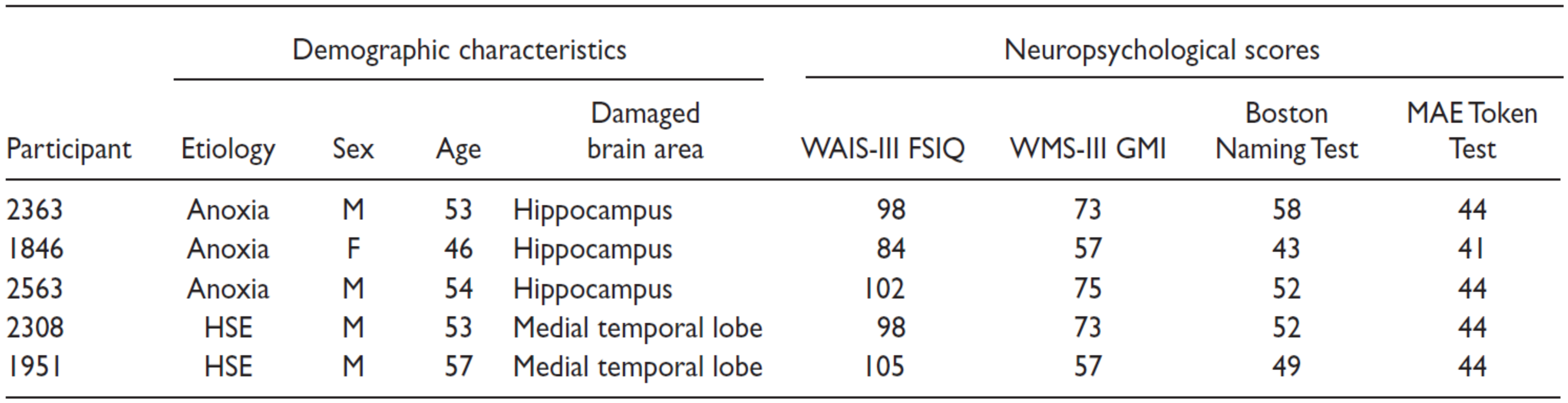
More striking and consequential, perhaps, than the amnesic participants’ failure to use common ground following a filled delay was their apparent success at resolving ambiguity in both of the visual conditions and in the linguistic no-delay condition, despite lingering fixations to competitor objects. Although amnesic, these individuals have normal intellectual and reasoning abilities and can take advantage of available information to guide behavior. The amnesics likely relied on external memory cues (see, e.g., Ballard, Hayhoe, & Pelz, 1995) in the visually unambiguous condition and information in the recent-discourse history in the linguistic no-delay condition to assess common-ground status. This result may also provide some support for arguments that there are other nondeclarative routes to forming common ground through priming or associations (Horton & Gerrig, 2005a, 2005b; Pickering & Garrod, 2004).

The pervasiveness of ambiguity in language is one of its most notable characteristics (Altmann, 1998) - in conversation, up to 50% of definite noun phrases are linguistically ambiguous (Brown-Schmidt & Tanenhaus, 2008). The fact that amnesic participants were able to use information available to them to resolve these ambiguities online speaks to their ability to rapidly extract information from the environment and apply it to abstract linguistic processes. This finding is in contrast to previous observations of the amnesic patient H. M., who was found to have tremendous difficulty in appreciating linguistic ambiguity (MacKay et al., 1998). The source of the difference is likely related to the use of very different procedures and measures, although H. M.'s comparably worse health, due to years of treatment for epilepsy, is also relevant. It is notable, as well, that the amnesic participants in the study reported here were able to represent items in common ground, suggesting that amnesic participants who learned names for novel shapes in our previous work (Duff et al., 2006) can in fact establish common ground for these names. That these same amnesic participants did not consistently use a definite reference (e.g., “the Viking ship”) to signal to their partner that these labels were part of shared knowledge further supports the notion of multiple forms of common ground with representational contributions from distinct memory systems (Duff, Gupta, Hengst, Tranel, & Cohen, 2011).

How successful, then, are patients with severe declarative memory impairment in communication with a conversational partner? There are, of course, many ways to measure success. Amnesic participants did successfully arrive at the correct interpretation of the experimenter's ambiguous instruction. However, although successful, participants had subtle deficits, as evidenced by lingering fixations to competitor objects. The source of this impairment may be the demand that language processing places on representations supporting online processing. Neurologically intact adults typically understand spoken (or signed) language with ease, rapidly integrating numerous sources of information (acoustic, syntactic, semantic, and pragmatic) to constrain potential ambiguities (Allopenna et al., 1998; Garnsey, Pearlmutter, Myers, & Lotocky, 1997; Kamide, Altmann, & Haywood, 2003; Tanenhaus, Spivey-Knowlton, Eberhard, & Sedivy, 1995). These processes are central to language understanding and have been explored only coarsely in amnesics using explicit tasks and off-line measures that cannot tap the incremental interpretation of words over time (e.g., Duff et al., 2007; MacKay et al., 1998). The current results reveal deficits in the integration of multiple information sources during online resolution of linguistic competition, and they allow us to make the strong claim that declarative memory mediation is necessary for online resolution of competition in language. In support of this hypothesis are parallel findings from the visual domain that show impairment in amnesic participants even in no-delay and short-delay conditions when mediation of multiple, related representations in real-time is required to pick a target among competitors (Barense, Gaffan, & Graham, 2007; Hannula, Tranel, & Cohen, 2006; Warren, Duff, Tranel, & Cohen, 2010).

The present research explored questions about the interface of memory and language in the most basic form of language use (i.e., conversation). Our approach to these questions provided insights not only about the role of declarative memory in using common ground, but also its role in the online resolution of competition during language processing and possibly beyond. We have demonstrated that successful use of common ground across time requires the maintenance of declarative memory representations. We have also documented that individuals with declarative memory impairment can form and use representations of items in common ground, as long as this information remains readily available. Finally, we have provided initial, tantalizing evidence that hippocampal mediation is necessary for the resolution of competition in online tasks. Deficits in amnesics in online language processing (i.e., even in the absence of any imposed delays) open up questions about unexpectedly significant challenges they may face in real-world language abilities. Future research will show what other aspects of language processing and other cognitive domains might be similarly sensitive to amnesia and hence dependent on declarative memory processes.

Table



	Demographic characteristics				Neuropsychological scores			
Participant	Etiology	Sex	Age	Damaged brain area	WAIS-III FSIQ	WMS-III GMI	Boston Naming Test	MAE Token Test
2363	Anoxia	M	53	Hippocampus	98	73	58	44
1846	Anoxia	F	46	Hippocampus	84	57	43	41
2563	Anoxia	M	54	Hippocampus	102	75	52	44
2308	HSE	M	53	Medial temporal lobe	98	73	52	44
1951	HSE	M	57	Medial temporal lobe	105	57	49	44

Table 4.1. Demographic and Neuropsychological Data for Participants with Amnesia. Note: Neuropsychological scores include Full Scale IQ (FSIQ) from the Wechsler Adult Intelligence Scale - Third Edition (WAIS-III; Wechsler, 1997a), General Memory Index (GMI) from the Wechsler Memory Scale - Third Edition (WMS-III; Wechsler, 1997b), score on the Boston Naming Test from the Boston Diagnostic Aphasia Examination (Goodglass & Kaplan, 2000; maximum score = 60), and score on the Multilingual Aphasia Examination (MAE; Benton, Hamsher, & Sivan, 1994; maximum score = 44). HSE = herpes simplex encephalitis; M = male; F = female.

Figures

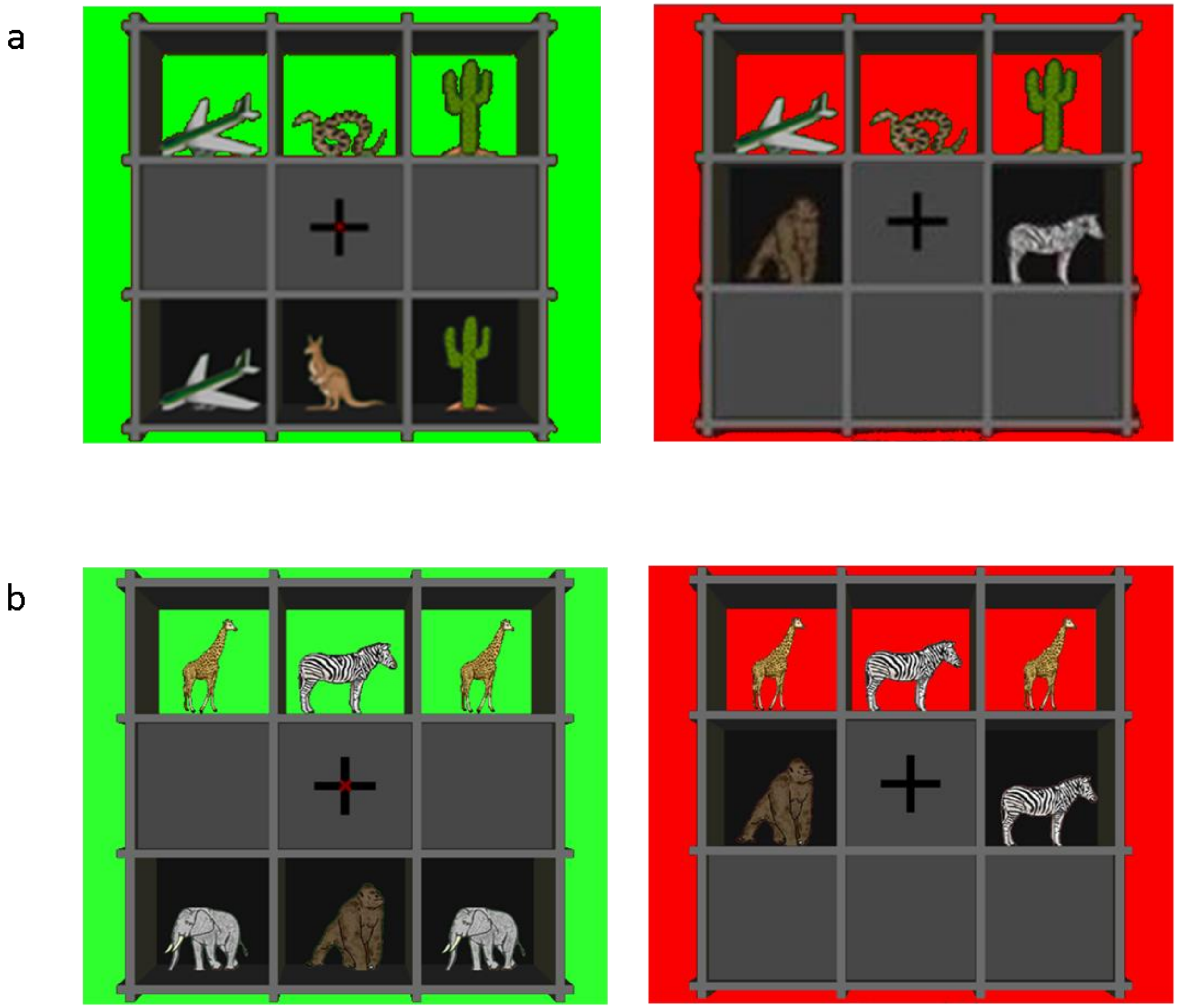


Figure 4. 1. Examples of the displays viewed by participants (left column) and the experimenter (right column) in the visual common-ground conditions. Each display consisted of a 3 × 3 grid of cubbyholes with a fixation cross in the center. Objects shared between the participant and the experimenter were presented in open cubbyholes in the top row. Objects that could be seen by only the participant or only the experimenter (i.e., privileged objects) were hidden by closed cubbyholes in the display’s bottom row and middle row, respectively. In visually unambiguous displays (a), a target object (in this example, the cactus) was presented once among the shared objects and once among the participant’s privileged objects. In visually ambiguous displays (b), a target object (in this example, the giraffe) was presented twice among the shared objects. The same displays used in the visual ambiguous condition were also used in the two linguistic common-ground conditions.

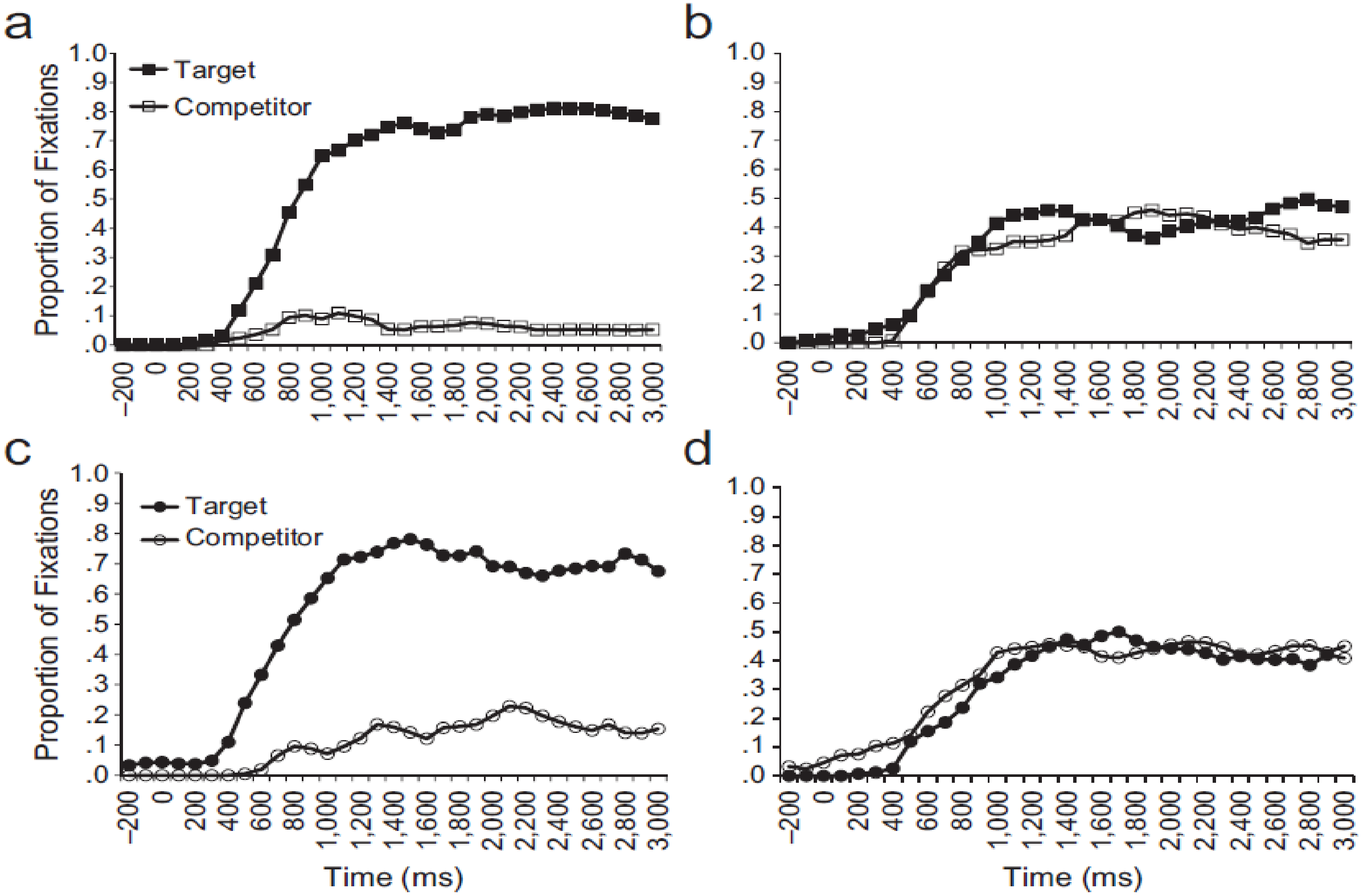


Figure 4. 2. Results for the visual common-ground conditions: proportion of fixations to targets and to competitor objects as a function of time. Time 0 is the onset of the critical word. Results are shown separately for healthy comparison participants in (a) the visually unambiguous condition and (b) the visually ambiguous condition and for amnesic participants in (c) the visually unambiguous condition and (d) the visually ambiguous condition.

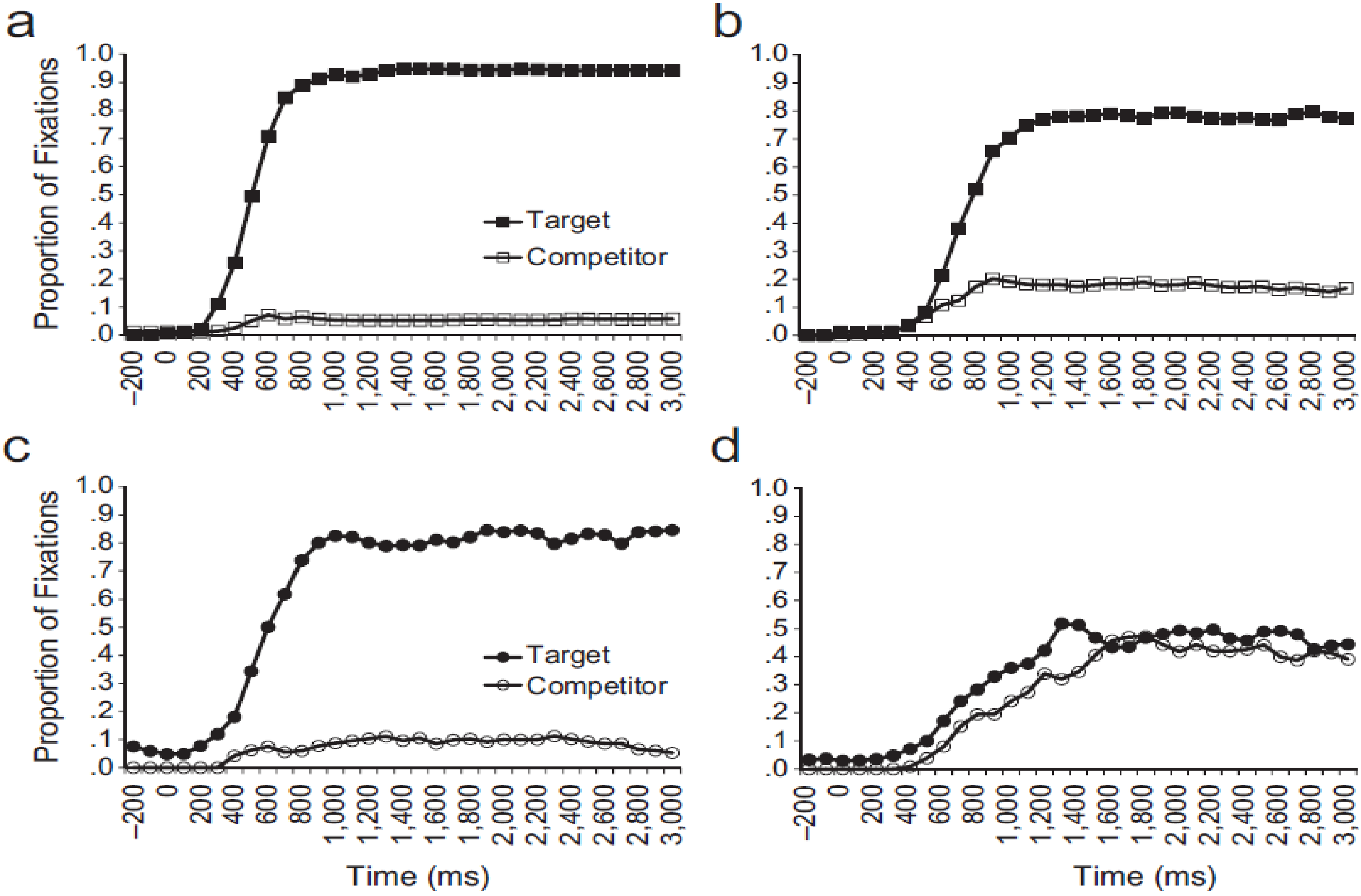


Figure 4.3. Results for the linguistic common-ground conditions: proportion of fixations to targets and to competitor objects as a function of time. Time 0 is the onset of the critical word. Results are shown separately for healthy comparison participants in (a) the no-delay condition and (b) the filled-delay condition and for amnesic participants in (c) the no-delay condition and (d) the filled-delay condition.

CHAPTER 5: HIPPOCAMPAL AMNESIA DISRUPTS CREATIVE THINKING[6]

Abstract

Creativity requires the rapid combination and recombination of existing mental representations to create novel ideas and ways of thinking. The hippocampal system, through its interaction with neocortical storage sites, provides a relational database necessary for the creation, updating, maintenance, and juxtaposition of mental representations used in service of declarative memory. Given this functionality, we hypothesized that hippocampus would play a critical role in creative thinking. We examined verbal and figural creative thinking, as measured by the Torrance Tests of Creative Thinking (TTCT), in a group of participants with hippocampal damage and severe declarative memory impairment as well as in a group of demographically matched healthy comparison participants. The patients with bilateral hippocampal damage performed significantly worse than comparison participants on both the verbal and figural portions of the TTCT. These findings suggest that hippocampus plays a role critical in creative thinking, adding to a growing body of work pointing to the diverse ways the hallmark processing features of hippocampus serve a variety of behaviors that require flexible cognition.

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[6] This chapter has been submitted and is under review. It is referred to later in this document as “Duff, Kurczek, Rubin, Cohen, & Tranel, 2013”. Duff, M.C., Kurczek, J., Rubin, R., Cohen, N.J., & Tranel, D. (2013). *Hippocampal amnesia disrupts creative thinking*. Manuscript submitted for publication.

Ancient Grecian and Roman scholars and philosophers attributed creativity to divine inspiration (Albert & Runco, 1999). Today creativity is considered a quintessential and uniquely human characteristic of considerable interest to researchers in psychology and cognitive neuroscience (e.g., Andreasen, 2005; Damasio, 2001; Dietrich, 2004; Heilman, 2005). A precise definition of creativity is not universally agreed upon, yet several researchers have characterized aspects of creativity thinking. Creativity has been thought of as the ability to produce ideas or responses that are both novel (i.e. original, rare, and unexpected) and appropriate (i.e. adaptive and useful given task constraints) (Flaherty, 2005; Sternberg & Lubart, 1999). Creativity has also been described as the "epitome of cognitive flexibility" (Dietrich, 2004, p. 1014), requiring the rapid combination and recombination of existing mental representations to create novel ideas and ways of thinking (Bristol & Viskontas, 2006). Similarly, Damasio (2001) states that the processes of creativity include the *generation* of representational diversity, *manipulation* of this representational diversity, and *recognition* of *novel* representations that when combined result in creative thinking.

Much of the work linking creativity to the brain has focused on the frontal lobes, which is understandable given the known roles of the frontal lobes in processes such as cognitive flexibility, fluency, and abstract reasoning (cf. Gläscher et al., 2012). For example, there is evidence of changes in creativity in psychiatric conditions where frontal lobe pathology is observed (e.g., schizophrenia; Folley & Park, 2005) and cognitive studies of creativity point to the collection of abilities putatively associated with the frontal lobes (e.g., working memory, abstraction, fluency, reasoning, flexibility) (Bogousslavsky, 2005; Dietrich, 2004; Runco, 2004). fMRI studies also report prefrontal cortex activation in tasks of creativity (e.g., Dietrich & Kanso, 2010; Kowatari et al., 2009).

Another less acknowledged brain structure that appears well suited to us to contribute to creativity is hippocampus and that is the focus of the current study. For example, we have been intrigued that definitions of creativity typically refer to processes such as the rapid generation, combination, and recombination of existing mental representations to create novel ideas and ways of thinking (Bristol & Viskontas, 2006; Damasio, 2001). These descriptions are remarkably similar to various processing features of hippocampal function. Hippocampus has been described as the critical structure in the brain that serves as a relational database to create, update, and juxtapose mental representations that form the basis of declarative memory (Cohen & Eichenbaum, 1993; Eichenbaum & Cohen, 2001). Characteristic features of hippocampal processing include the ability to form arbitrary relations and bind together distinct aspects of experience, in addition to interacting with neocortical storage sites to support integration and flexible use of representations to optimize performance under a variety of circumstances (Bunsey & Eichenbaum, 1996; Eichenbaum & Cohen, 2001; Gabrieli, 1998; O'Keefe & Nadel, 1978; Squire, 1992).

The role of hippocampus is well established in forming and recollecting new declarative memories; however, recent evidence suggests hippocampus also contributes to maintenance and on-line processing of relational information. Participants with hippocampal amnesia show deficits across minimal delays and even when all the necessary information is immediately available (e.g., Barense, Gaffan, & Graham, 2007; Hannula, Tranel & Cohen, 2006; Warren, Duff, Tranel, & Cohen, 2011; Rubin, Brown-Schmidt, Duff, Tranel & Cohen, 2011). These results converge with fMRI findings of hippocampal activation for declarative memory over the same short delays (e.g., Hannula & Ranganath, 2008; Ranganath & D'Esposito, 2001). Such findings encourage the idea that hippocampus processes relational information on the time-scale necessary to rapidly generate, combine, and recombine mental representations, which are essential aspects of creative thinking (Bristol & Viskontas, 2006; Damasio, 2001). Although creative thinking has not been formally examined in hippocampal amnesia, other work links hippocampal damage to impairments in imagining events (Hassabis, Kumaran, Vann, & Maguire, 2007) and to disruptions in the creative use of language (Duff, Hengst, Tranel, & Cohen, 2009). We hypothesize that the characteristic relational processing features of hippocampus support aspects of creativity, and, accordingly, that hippocampus plays an important role in both verbal and figural creative thinking.

We used a neuropsychological approach to test this proposal. Five patients with bilateral hippocampal damage (hereafter, AM group, for "amnesic") completed the nationally normed *Torrance Tests of Creative Thinking* (TTCT). Table 5.1 presents demographic, anatomical, and neuropsychological information for the amnesic participants. The amnesic patients have a severe and selective declarative memory impairment, as revealed by their respective WMS-III GMI score, yet generally intact scores on other measures of executive function, intelligence, language, and perception. Additional measures of frontal lobe function also reveal generally preserved abilities in these patients (see Konkel, Warren, Duff, Tranel, & Cohen, 2008). We also collected data from 10 healthy comparison participants (hereafter, NC group, for "normal comparisons") matched to amnesic participants on age, sex, handedness, and education.

The TTCT has been used widely in the study of creativity (Colangelo & Davis, 1991; Lissitz & Willhoft, 1985) and has undergone significant investigation (e.g., Chase, 1985; Clapham, 1998; Dixon, 1979; Heausler, & Thompson, 1988). The TTCT has a verbal and figural form (booklet A for both tests was administered). The verbal form consists of six timed (five to ten minutes) subtests requiring participants to use written language to ask questions about a picture of an event, guess causes and consequences (immediate or long-term) of an action in a picture, generate ways to improve a toy so that it is more fun to play with, generate alternative uses for a common object (e.g., a cardboard box), and generate hypotheses about potential benefits or problems related to an improbable situation (e.g., if clouds had strings attached to them). For each task, participants listed as many responses as they could during the time allotted.

The figural form consists of three timed (ten minutes) subtests requiring participants to create novel drawings constructed from varying degrees of partial information (e.g., one large oval-shaped figure; ten novel partially incomplete line contours; 30 repeated parallel line segments). For each task, participants were instructed to create meaningful drawings from the incomplete figure and give each drawing a unique title. For both the verbal and figural forms, instructions and materials were visible at all times (eliminating explicit demands on memory). If a participant stopped or indicated they could not think of anything else, the examiner informed the participant they had more time and encouraged them to keep thinking. To ensure consistency and unbiased scoring, test forms were sent to the publisher for standardized scoring. Standard scores for overall verbal and figural performance were calculated, including various dimensions of verbal (e.g., fluency, flexibility, originality) and figural (e.g., fluency, resistance to premature closure, elaboration, abstractness of title, and originality) performance[7].

On the verbal portion, the composite verbal score for healthy comparison participants (*M* = 101.7; *SD* = 24.6) was significantly higher than amnesic participants (*M* = 57.0; *SD* = 8.3) (*F*(1, 13) = 15.17, *p* = 0.002; see Figure 5.1). This same pattern was observed for all three of the verbal dimensions including: fluency (NC: *M* = 101.3; *SD* = 29.3; AM: *M* = 54.6; *SD* = 8.6; *F*(1,

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[7] Fluency = number of interpretable, meaningful and relevant ideas; Flexibility = the number of different categories of relevant responses; Originality = the number of statistically infrequent ideas; Resistance to premature closure = The degree of psychological openness (i.e. to consider a variety of options and keep an "open mind"); Elaboration = the number of added ideas; Abstractness of titles = The degree beyond labeling (i.e. abstraction of thought).

13) = 11.76, *p* = 0.004), flexibility (NC: *M* = 93.9; *SD* = 21.4; AM: *M* = 49.4; *SD* = 9.8; *F*(1, 13) = 19.05, *p* = 0.0008), and originality (NC: *M* = 110.7; *SD* = 24.6; AM: *M* = 63.0; *SD* = 10.6; *F*(1, 13) = 16.32, *p* = 0.001). Representative responses are included to illuminate the difference in performance between the groups. For example, when asked to think of creative uses for cardboard boxes, healthy comparison participant matched to amnesic participant 2363 produced 26 uses, 23 of which were determined to be unique (e.g., including building a suit of armor). In sharp contrast, amnesic participant 2363 produced only 2 uses (e.g., recycling the boxes and making a fort).

On the figural portion, the composite figural score for healthy comparison participants (*M* = 101.8; *SD* = 12.2) was significantly higher than amnesic participants (*M* = 74.6; *SD* = 17.5) (*F*(1, 13) = 12.48, *p* = 0.004; see Figure 5.1). This pattern was observed on four of the five figural dimensions including: fluency (NC: *M* = 97.3; *SD* = 18.6; AM: *M* = 68.4; *SD* = 21.0; *F*(1,13) = 7.41, *p* = 0.02), originality (NC: *M* = 92.6; SD = 18.01; AM: *M* = 64.8; *SD* = 17.2; *F*(1, 13) = 8.1, *p* = 0.01), titles (NC: *M* = 110.0; *SD* = 10.1; AM: *M* = 78.0; *SD* = 28.7; *F*(1, 13) = 10.5, *p* = 0.006), and elaboration (NC: *M* = 105.2; *SD* = 14.2; AM: *M* = 71.8; *SD* = 10.0; *F*(1, 13) = 21.91, *p* = 0.0004). On the resistance to premature closure dimension, there was no significant difference (*F*(1, 13) = 2.1, *p* = 0.17) between comparison (*M* = 104.1; *SD* =14.7) and amnesic (*M* = 89.6; *SD* = 24.4) participants. Again, representative examples are included to illustrate the difference in performance between the groups. In the figural subtest where participants were presented with a large oval-shape figure and asked to think of a picture that includes this shape, adding new ideas to make the picture tell as interesting and exciting a story as possible drawings from two amnesic participants (1951 and 1846) and their matched healthy comparison participants are presented in Figure 5.2. One comparison participant used the oval as part of a golf course complete with signs for parking and the clubhouse, the CBS sports truck, the fairway, a sand trap, and Tiger Woods with his caddy. The other comparison participant made the oval into a giant tick or “tick-mobile” that, similar to hot air balloons, takes people for rides above the city where people stood in line for the ride. In sharp contrast, given the same stimulus and the full 10 minutes, amnesic participant 1951 turned the oval into a bug and amnesic participant 1846 used the shape as an egg and drew a chicken above it. The richness of the contextual details provided by the healthy comparison participants, and the lack of them in the productions of the amnesic participants, is reminiscent of the well-documented deficit in episodic memory in amnesia. Theoretical accounts of hippocampal function such as cognitive map theory (O’Keefe & Nadel, 1978) and scene construction theory (Hassabis & Maguire, 2007) resonate with the performance of the amnesic participants on the figural portion of the TTCT, in that these ideas emphasize the role of hippocampus in spatial processing; however, they do not account for the deficit of the amnesic participants on the verbal portion (which was greater than the deficit on the figural portion).

The poor performance of patients with hippocampal amnesia on *both* the verbal and figural portions of the TTCT provides preliminary support for our proposal that the hippocampus plays a critical role in creative thinking. Decades of research have linked the functionality of the hippocampus, including its capacity for supporting relational binding and representational flexibility, to the formation and subsequent retrieval of declarative memory (e.g., Bunsey & Eichenbaum, 1996; Eichenbaum & Cohen, 2001; Gabrieli, 1998; O’Keefe & Nadel, 1978; Squire, 1992). We propose this same functionality of hippocampus is used in service of creative thinking, i.e., the process of rapidly generating, combining, and recombining existing mental representations in the moment to create something new, regardless of the nature of the materials.

These findings are in line with work suggesting that the relational binding and representational flexibility afforded by the hippocampus contribute to capacities akin to creativity such as inferential reasoning (logical process by which elements of individual existing memories are retrieved and recombined to answer novel questions) (Zeithamova, Schlichting, & Preston, 2012), future thinking (e.g., Addis & Schacter, 2012), making comparisons (Olsen, Moses, Riggs, & Ryan, 2012), and verbal play (Duff et al., 2009). Given the absence of any explicit demands on memory (e.g., no delays; when all the stimuli remain in view) these results highlight a disruption in creativity attributed to hippocampal damage, beyond the classical memory deficit observed in amnesic participants.

Could other aspects of amnesic participants' neuropsychological profiles account for these findings? For example, previous work has suggested a connection between IQ and creativity (e.g., Barron, 1963). While we cannot address this directly with our entire data set (we do not have IQ data on all comparison participants), the TTCT is a nationally normed test with data from tens of thousands of participants. Assuming a normal distribution of IQ scores across this large sample, amnesic participants (who all have IQs in the normal range as measured by the Wechsler Adult Intelligence Scale) are still significantly impaired relative to the national sample. Compared to national norms, on the verbal portion of the TTCT, amnesic participants (as a group) have a standard score of 57 placing them in the 3rd percentile nationally (range = 1st-7th percentile). On the figural portion of the TTCT amnesic participants have a standard score of 74 placing them in the 13th percentile nationally (range = 1st - 42nd percentile). Furthermore, there was not a significant correlation between amnesic participants' IQ and their performance on either the verbal ($r(3) = -0.33$, $p = 0.58$) or figural ($r(3) = -0.61$, $p = 0.27$) portions of the TTCT.

The notion that IQ is not a significant factor in creative thinking is consistent with a recent meta-analysis of 21 studies reporting a negligible relationship between creativity and IQ (Kim, 2005).

Other aspects of cognition frequently linked to creativity (e.g., generation, construction, abstraction, fluency) can be captured by some standardized neuropsychological assessments (Lezak, Howieson, Bigler, & Tranel, 2012). While neuropsychological measures reveal disproportionate memory impairments in amnesia (see Table 5.1), it is not surprising to see lower performance on certain measures outside the domain of memory. For example, amnesic participants have depressed scores on verbal category fluency (COWA); the ability to generate a number of relevant or related items (e.g., words that begin with the same letter). One amnesic participant with damage beyond hippocampus and two amnesic participants with damage limited to hippocampus have scores that are two standard deviations below the mean. This appears very much akin to the amnesic participants significantly lower scores on the TTCT fluency dimension (verbal and figural). Fluency, or the quantity of responses produced, however, is only one aspect of creative thinking. Individual responses, even a few, could be deemed creative if highly unusual or richly detailed and elaborated (perhaps captured by the TTCT dimensions of originality or elaboration). Indeed, amnesic participant 1846 has a COWA score two standard deviations below the mean (see Table 5.1), yet scores the highest among all amnesic participants on both verbal and figural creativity tests.

Creativity is among the most complex of human behaviors. Our findings suggest that hippocampus plays a role in the rapid generation, combination, and recombination of existing mental representations that are available for and processed in concert with other neural systems in service of creative thinking. Linking deficits in creative thinking to hippocampal dysfunction adds to a growing body of work pointing to the diverse ways the characteristic processing features of hippocampus serve a variety of cognitive domains. Finally, the results support the idea that the neural basis of creativity extends beyond the more oft-mentioned frontal lobes to include the hippocampus.

Table

	Demographic		**Anatomical**			**Intelligence**			**Memory**	**Language**			**Perception**	**EF**	
AM	**Age**	**Ed**	**Etiology**	**Lesion**	**HC Volume**	**WAIS-III FSIQ**	**WAIS-III VIQ**	**WAIS-III PIQ**	**WMS-III GMI**	**BNT**	**TT**	**COWA**	**CFT Copy**	**WCT PE**	**WCT Cat**
1846	46	14	Anoxia	Bilateral HC	-4.23	84	88	86	**57**	43	41	**24**	28	6	6
1951	57	16	HSE	Bilateral HC + other MTL	-8.10	106	107	106	**57**	49	44	40	32	16	6
2308	53	16	HSE	Bilateral HC + other MTL	N/A	95	96	78	**45**	52	44	**16**	32	N/A	N/A
2363	53	16	Anoxia	Bilateral HC	-2.64	98	112	91	**73**	58	44	26	26	12	6
2563	54	16	Anoxia	Bilateral HC	N/A	94	91	103	**63**	52	44	**21**	36	6	6
Mean (SD)	52.6 (4.0)	15.6 (1.7)			-4.99 (2.8)	95.4 (7.9)	98.8 (10.3)	94.8 (14.9)	59.0 (10.2)	50.8 (5.5)	43.4 (1.3)	25.4 (9.0)	30.8 (3.9)	10.0 (4.9)	6 (0.0)

Table 5.1. Amnesic Participant's Demographic, Anatomical and Neuropsychological Characteristics Note. Ed. = education; HSE = Herpes Simplex Encephalitis; HC = Hippocampus; MTL = Medial Temporal Lobe; HC Volume = hippocampal volumes obtained using high-resolution volumetric MRI (as studentised residual differences with hippocampal volume z-scores), revealing significantly reduced hippocampal volumes relative to a matched comparison group (Allen, Tranel, Bruss, & Damasio, 2006; Buchanan, Tranel, & Adolphs, 2005); Bolded scores are impaired, defined as 2 standard deviations from the mean on each test; WAIS-III = Wechsler Adult Intelligence Scale-III; FSIQ = Full Scale Intelligence Quotient; VIQ = Verbal Intelligence Quotient; PIQ = Performance Intelligence Quotient; WMS-III = Wechsler Memory Scale-III; GMI = General Memory Index; BNT = Boston Naming Test; TT = Token Test; COWA = Controlled Oral Word Association; COWA score is summed over F, A, and S; CFT = Complex Figure Test; EF = Executive Functions; WCT = Wisconsin Card Sorting Task; PE = Perseverative errors; Cat = Number of categories achieved out of six.

Figures

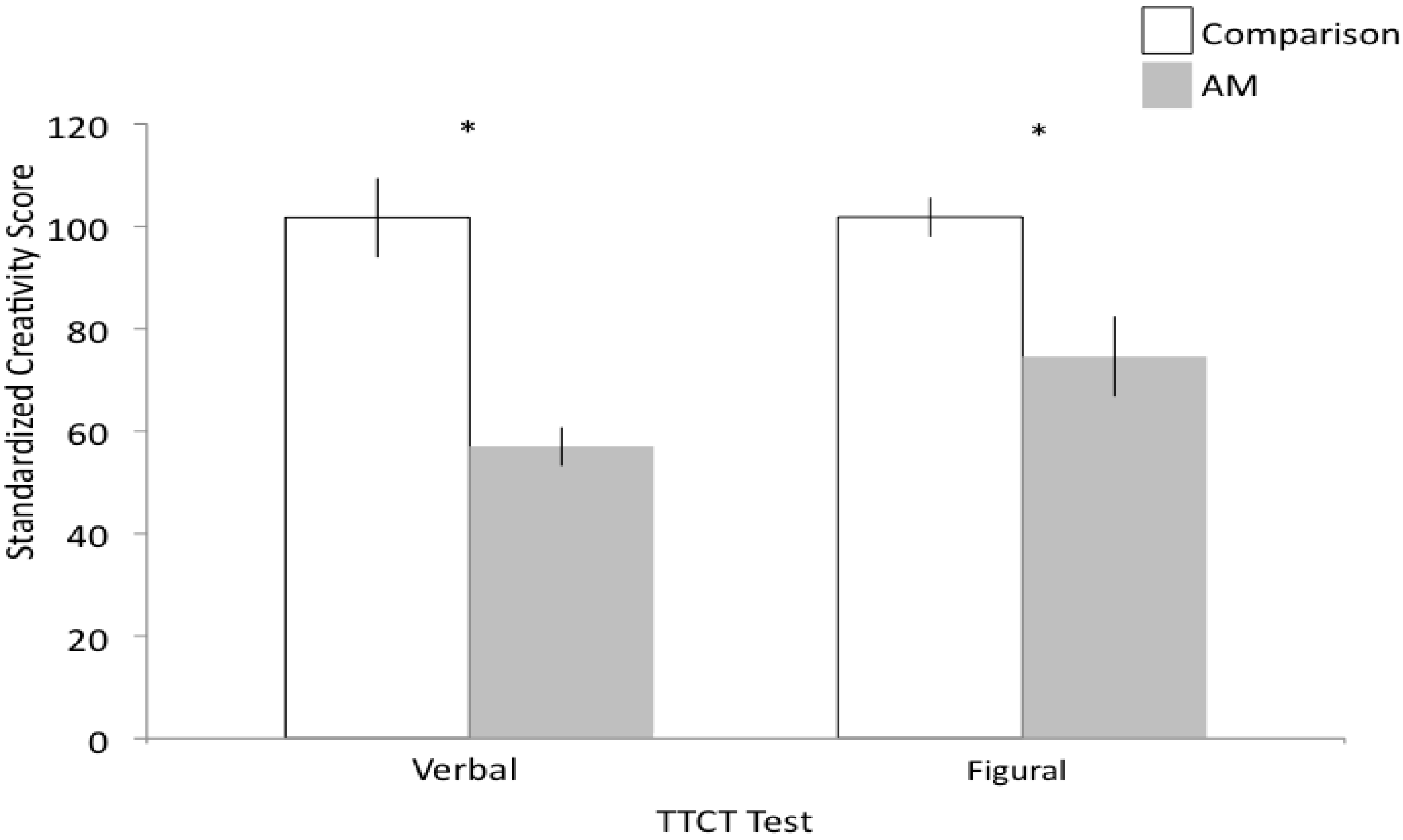

Figure 5. 1. Performance on Verbal and Figural Forms of TTCT. Means and standard error; *Indicates significant ($p < 0.05$) differences between groups.

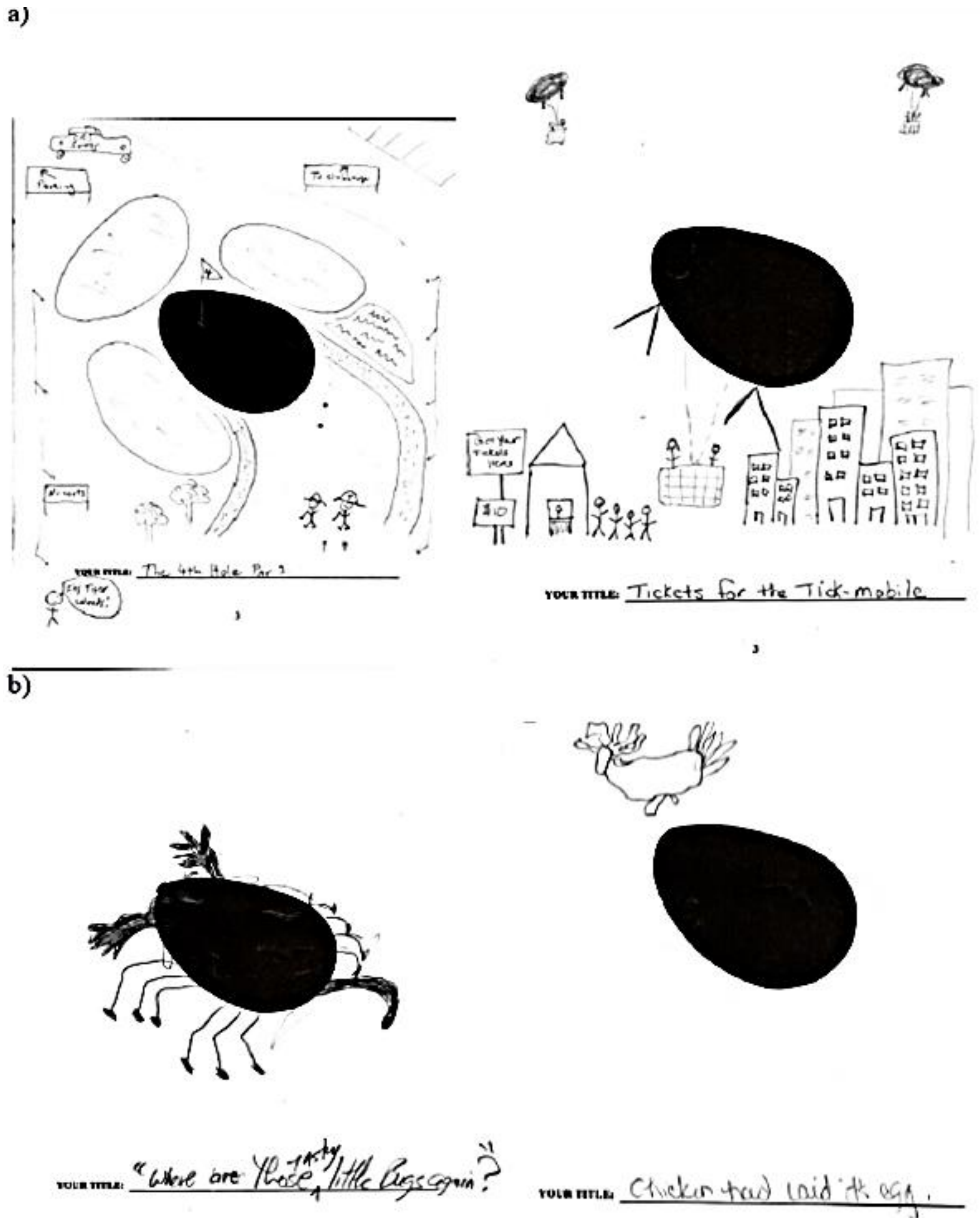

Figure 5.2. Figural Subtest: 1 Picture Construction from Oval Stimulus. Note: A: Comparison participant – Title: The 4th Hole Par 3; notations read from upper left clockwise: To parking; To clubhouse; Its Tiger Woods!; No carts; B: Comparison participant – Title: Tickets for the tick mobile; notations read Get your tickets here; $10; C: Amnesia participant 1951 – Title: Where are those tasty little buggers?; D: Amnesia participant 1846 – Title: Chicken had laid its egg.

CHAPTER 6: NEW IDEAS ABOUT MEDIAL TEMPORAL LOBE (MTL)

Memory Representations Supported by MTL

Memory is one of the most intriguing aspects of the human mind. Debate about different types or kinds of memory has existed for literally hundreds of years. Only recently, however, have scientists had the necessary tools to characterize memory systems in the human brain. The approach of cognitive neuroscientists has been to study the functional characteristics of different brain regions to better understand and describe the structure of human memory.

Neuropsychological data from individuals with medial temporal lobe (MTL) amnesia led to the first structure-based distinction between memory systems in the human brain. Since MTL damage caused (1) profound impairments in forming new long-term memories (LTM) and (2) other kinds of procedural and short-term memories (STM) appeared intact, many supported the neuroanatomical distinction between LTM and STM (see Squire et al., 1993). This characterization suggested cognitive abilities that take place on the time scale of STM do not engage MTL.

Other researchers, however, characterized MTL function in terms of the kinds of representations that individual sub-regions supported, not by the length of delay necessitating either long-term or short-term memory. Relational memory theory characterized the functional contribution of MTL in proposing that hippocampus and perirhinal cortex support different kinds of memory representations (Cohen & Eichenbaum, 1993; Eichenbaum & Cohen, 2001). Hippocampus supports **relational memory** (i.e. binding <u>arbitrarily</u> related information and permitting its flexible use), while perirhinal cortex supports **item memory** (i.e. binding of inflexible relations - i.e. fused, unitized or configural representations).

This characterization of MTL function anticipated the possibility that hippocampus is critical to tasks that place a sufficient demand on relational representations, regardless of delay or timescale. The idea that hippocampus is involved in supporting relational representations on the timescale of STM has been shown to be true in many different paradigms (Barense et al., 2007; Hannula et al., 2006; Olson et al., 2006; Olson et al., 2006; Watson, et al., 2013). Strong evidence of hippocampal involvement during on-line relational processing has also been shown in eye-movements (as a measure of on-line processing) in participants with hippocampal amnesia.

Warren and colleagues observed deficits in participants with hippocampal amnesia on several tasks involving relational processing, even when all necessary information remained available (Warren et al., 2010, 2011). In Warren et al. (2011), a target stimulus remained in the center of the screen while participants searched for the matching stimulus in a display filled with similar competitor stimuli. All target stimuli were circles composed of three uniquely patterned slices, while competitor stimuli were circles composed of one, two, or three matching patterned slices. Despite the task having no imposed delay, eye-movement measures in individuals with hippocampal damage showed abnormally rapid degradation of target representations. This effect manifested despite shorter searches and more frequent fixations to the target, demonstrating the contribution of hippocampus in maintaining relational information during on-line processing of uniquely patterned visual stimuli.

Yet, questions remained as to whether the kinds of representations supported by individual MTL sub-regions (i.e. hippocampus and perirhinal cortex) are involved in on-line processing during tasks which are commonly considered outside the domain of memory. In Chapter 3, we investigated whether perirhinal cortex supports inflexible, fused representations during a visual task, using a novel brain imaging approach: fMR-adaptation (Rubin et al., 2013). In Chapter 4, we investigated whether participants with hippocampal amnesia could form and use common ground in a psycholinguistic paradigm, by monitoring eye-movements to assess the ability to relate arbitrary pieces of information (Rubin et al., 2011). In Chapter 5, we investigated whether hippocampus contributes to the flexible use of information, as revealed by performance of participants with hippocampal amnesia on verbal and figural tests of creativity (Duff et al., 2013).

Perirhinal Cortex Supports Fused Perceptual Representations

Relational memory theory suggests that hippocampus supports arbitrary, flexible relations while its surrounding cortices, namely perirhinal cortex, support binding of inflexible relations - i.e. fused, unitized, or configural representations (Cohen & Eichenbaum, 1993; Cohen et al., 1997; Konkel et al., 2008). In Chapter 3, we investigated the role of perirhinal cortex proposed by relational memory theory, in binding visual representations of fused item features prior to the involvement of hippocampal binding mechanisms, using the imaging technique of fMR-adaptation.

We manipulated the particular combination of visual forms that composed an object to bias the perception of a set of abstract features as either a single fused object or two separate objects. The critical comparison was between the condition in which the same fused object was presented across the duration of the trial (i.e. Fused item condition) to the condition in which a non-fused variant of two visual forms was presented immediately followed by a fused variant of the same visual forms (i.e. Paired item condition).

(1) The findings revealed that perirhinal cortex generated a novel response to the presentation of the fused object, even when the same two visual forms had just been presented as separate (i.e. non-fused) visual forms. Thus, perirhinal cortex supports specific combinations of item features as a fused object representation, not simply the visual similarities between the objects. This result is the first to provide evidence showing perirhinal cortex supports fused item representations in humans.

One implication of this result is that perirhinal cortex forms representations taking into account the information driving perception - in this case, either a single object versus two separate objects moving together or separately, and perhaps other gestalt visual principles such as spatial contiguity. This account of perirhinal cortex is consistent with Bussey, Saksida, & Murray (2002, 2005), which emphasize its role in visual representation of complex objects, as well as Cohen and Eichenbaum (1993), which emphasize its role in representation of fused item (or generally inflexible) representations.

(2) The findings establish that fMR-adaptation can be used to show differences in complex item representations throughout the visual system and early MTL regions, as revealed by adaptation or recovery from adaptation to a set of repeated stimuli. An intriguing possibility is that the adaptation technique could also be used as a marker of online unitization in situations that require the volitional combination of spatially discontiguous items - more akin to the studies that address the role of unitization in associative memory (e.g., Diana, Van den Boom, Yonelinas, & Ranganath, 2011; Haskins, Yonelinas, Quamme, & Ranganath, 2008; Quamme, Yonelinas, & Norman, 2007).

Hippocampus Supports Arbitrary Relations during Common Ground

The dominant view of common ground representations is that when individuals encode information about events, they tag those memories with information about who was there and what each person's role was in the event (Clark & Marshall, 1978, 1981). This view of common ground emphasizes hippocampal-dependent representations in terms of the ability to support arbitrary relations regarding co-occurrence of people, places, and objects, along with the spatial, temporal, and interactional relations among them (Cohen & Eichenbaum, 1993; Eichenbaum & Cohen, 2001). Hence, in Chapter 4, we investigated the ability of participants with hippocampal amnesia to form and use arbitrary, relational representations to support common ground using a psycholinguistic paradigm.

In the task, each amnesic (or healthy matched comparison) participant jointly viewed scenes, in which the target object was in common ground and a visually identical competitor object was in privileged ground. If the amnesic participant represented common ground, the information could be used to resolve ambiguity between the target and visually identical competitor. We measured eye-movements to test the degree to which individuals with hippocampal damage could establish common ground and use it to guide on-line language comprehension. In this task, common ground was established from a single reference to a specific object, demanding the need for arbitrary, relational representations.

(1) Eye-movement measures demonstrated hippocampus was necessary to bind arbitrary relations to support linguistic common ground representations, even over short delays. Participants with hippocampal damage looked equally to the target and competitor object. They

did not know which object had previously been mentioned (and thus was in common ground), as the relationship between the target and competitor object was always arbitrary.

(2) Eye-movement measures also revealed a deficit in individuals with hippocampal amnesia during no-delay conditions. Amnesics made more looks to the competitor object, even when they were successful in directing the majority of their fixations to the target object. (The identity of the target was less arbitrary in the visual common ground condition since the presence of the target in visual common ground was always designated by a particular background color). When relational representations were required, nevertheless, to resolve linguistic competition and identify the particular object in common ground, impairments in on-line measures are evident in individuals with hippocampal amnesia. The findings also parallel deficits in the visual domain when mediation of multiple, related representations is required in real-time to pick a target among competitors (Barense et al., 2007; Hannula et al., 2006; Warren et al., 2010).

The findings emphasize the contribution of hippocampus in forming arbitrary relations to support common ground and guide on-line language processing. The evidence also indicates a clear role of declarative memory, which supports the classical view of common ground (Clark & Marshall, 1978, 1981). Hence, in individuals with hippocampal amnesia, the use of common ground is likely to be significantly impaired, since conversational use of common ground often relies on a single reference to a specific event, requiring relational representations of people, places, and objects, along with spatial, temporal, and interactional elements (Cohen & Eichenbaum, 1993; Eichenbaum & Cohen, 2001).

Hippocampus Supports Flexible Relations during Creative Thinking

In the domain of creativity, most researchers do not theorize about the contribution of hippocampus in supporting flexible, relational representations. Researchers focus on characterizing aspects of creative thinking, including (1) the ability to produce ideas or responses that are novel and appropriate (Flaherty, 2005; Sternberg & Lubart, 1999), (2) the rapid combination and recombination of mental representations to create new ideas (Bristol & Viskontas, 2006), (3) the ability to generate, manipulate, and recognize novel conceptual representations (Damasio, 2001), and (4) the use of cognitive flexibility (Dietrich, 2004). Even when generating potential anatomical candidates involved in creative thinking, the hippocampus is not mentioned. Instead, most researchers emphasize the contribution from the frontal lobes in the neural basis of creativity (Dietrich, 2004; Dietrich & Kanso, 2010; Heilman et al., 2003).

We were intrigued, however, that descriptions of creative thinking typically refer to cognitive processes that are remarkably similar to characteristic features of hippocampal processing. Hence, in Chapter 5, we investigated whether hippocampus supports flexible, relational representations in service of creating, updating, and juxtaposing mental representations for creative expression of information and ideas. To measure creativity in individuals with hippocampal amnesia, we used nationally normed tests of verbal and figural creativity - i.e. the Torrance Tests of Creative Thinking (TTCT).

(1) Standard scores for overall verbal and figural creativity were calculated on individual dimensions of verbal (e.g., fluency, flexibility, originality) and figural (e.g., fluency, resistance to premature closure, elaboration, abstractness of title, and originality) performance. The findings

demonstrated that individuals with hippocampal amnesia were impaired in the overall combined score for both verbal and figural measures of creativity.

Even on the individual dimensions, amnesics were impaired in all aspects of creativity - except the figural dimension of resistance to premature closure (i.e. to consider a variety of options and keep an "open mind"). In comparing measures of fluency, elaboration, abstractness of title, originality, and resistance to premature closure, resistance to premature closure seems to require the least flexible mental representations. On the figural portion only, this dimension is based on the amount of information <u>already</u> provided (e.g. incomplete line drawings) and therefore imposes less flexible manipulation of possible representations. On this measure, amnesics and comparisons perform similar.

(2) The finding also highlights the contribution of hippocampus during on-line processing. On every test of creativity, all materials were available to the participant and there were no imposed delays. Hence, even in the absence of an explicit memory demand, individuals with hippocampal damage demonstrated impairments in creativity. Impairments due to an inability to support <u>flexible</u>, relational representations and rapidly generate, combine, and recombine existing mental representations into creative ideas. Furthermore, this evidence extends the neural basis of creativity beyond the more oft-mentioned frontal lobes.

Characteristic Contributions of MTL to Many Domains

Guided by the insight of relational memory theory, experimental Chapters 3, 4, and 5 reveal characteristic contributions of MTL to domains of perception, language, and creativity. Relational memory theory offers a parsimonious, domain invariant account of MTL function. It anticipated the possibility that hippocampus is critical to tasks that place a sufficient demand on relational representations, regardless of delay, timescale, or domain. This understanding of representations supported by MTL sub-regions has advanced the field of cognitive neuroscience by sparking theory driven experimental investigations of hippocampal contributions to many cognitive tasks.

In neuropsychological studies of hippocampal amnesia, deficits have been observed across a variety of domains and timescales when the characteristic contributions of hippocampus (i.e. relational representations) are required. Impairments have been observed in: **complex decision-making** (Gupta, Duff, Denburg, Cohen, Bechara, & Tranel, 2009; Gutbrod, Krouzel, Hofer, Müri, Perrig, & Ptak, 2006), **character judgments** (Croft, Duff, Kovach, Anderson, Adolphs, & Tranel, 2010; Johnson, Kim, & Risse, 1985; Rubin, Duff, Tranel, & Cohen, 2010), **establishing and maintaining social bonds** (Davidson, Drouin, Kwan, Moscovitch, & Rosenbaum, 2012), **theory of mind when experiences of others are personally familiar** (Rabin, Carson, Gilboa, Stuss, & Rosenbaum, 2012), **generative and open-ended creative tasks** (Sheldon, Romero, & Moscovitch, in press), **spatial navigation** (Maguire, Nannery, & Spiers, 2006), **behavior-induced attitude change - i.e. cognitive dissonance** (Lieberman, Ochsner, Gilbert, Schacter, 2001), and **imagining** (Hassabis et al., 2007; Kwan, Carson, Addis, & Rosenbaum, 2010; Maguire, Vargha-Khadem, & Hassabis, 2010).

All of these tasks require relational representations supported by hippocampus. The nature of complex tasks requires forming arbitrary associations, flexibly updating representations and integrating information to meet task demands. For example, complex decision-making, character judgments, establishing and maintaining social bonds, spatial navigation and imagining, all require the contribution and orchestration of information from multiple cognitive systems. According to relational memory theory, this is exactly the function of hippocampus - (1) support the binding of arbitrarily related, discrete pieces of information, (2) permit the flexible expression of information, and (3) link converging inputs from various association cortices (Cohen & Eichenbaum, 1993; Eichenbaum & Cohen, 2001).

Approaches toward Future Methods and Novel Findings

The neuropsychological approach in hippocampal amnesia is a powerful method that has contributed to many new, exciting findings. It is responsible for establishing that a particular brain region is critically involved in a particular function of a well-designed experiment. The power of cognitive neuroscience, however, comes from using convergent tools to investigate the same theoretical question (Kwok, 2011; Rorden & Karnath, 2004), eliminating many of the limitations inherent to any technique used in isolation.

For example, a limitation of some neuropsychological studies is small sample size. Brain imaging, conversely, gathers extremely large amounts of data and measures the degree to which various brain regions are active. Brain imaging also is non-invasive and can be used in many different populations. However, results of “active brain regions” need to be interpreted with caution. Activation of a particular region may not be causally related, but instead correlated, with execution of a particular process (Poldrack, 2008; Rorden & Karnath, 2004)

Thus, it is encouraging that neuropsychological studies of hippocampal amnesia converge with evidence from brain imaging. Brain imaging has also demonstrated the engagement of hippocampus in a variety of tasks involving relational processing. Hippocampal involvement has been shown during: **theory of mind when experiences of others are personally familiar**

(Rabin & Rosenbaum, 2012), **spatial navigation** (Rosenbaum, Ziegler, Winocur, Grady, & Moscovitch, 2004; Spiers & Maguire, 2006), and **imagining** (Addis & Schacter, 2007; Addis et al., 2007).

While the power of cognitive neuroscience comes from using convergent tools to investigate the same theoretical question (Kwok, 2011; Rorden & Karnath, 2004), the greatest potential of cognitive neuroscience is in understanding that there are functionally connected networks in the brain working together to achieve complex cognition. The method of brain imaging has been exceptionally valuable in understanding that the involvement of a particular brain region is *not* isolated during a task. Rather the contribution of each brain region, especially one like MTL located in the middle of the brain, is to work in combination with other regions to facilitate complex behavior.

Emerging methods that measure the connectivity of networks in the brain reveal contributions from MTL. Recent research has focused on (1) the functional contribution of MTL and parietal lobe to characterize the relationship between memory and attention (Cabeza, Ciaramelli, Olson, & Moscovitch, 2008; Cabeza, Mazuz, Stokes, Kragel, Woldorff, Ciaramelli, Olson, & Moscovitch, 2011; Wagner, Shannon, Kahn, & Buckner, 2005), especially during tasks on the timescale of short-term memory (Fuster & Bressler, 2012; Ranganath, Cohen, Dam, & D'Esposito, 2004); and (2) the functional contribution of MTL and prefrontal cortex to characterize the relationship between memory and cognitive control during tasks on the timescale of short-term memory (Barbey, Koenigs, & Grafman, 2012; Fuster, 2000, 2009; Miller & Cohen, 2001) and the timescale of long-term memory (Simons & Spiers, 2003).

Conclusion

There are a multitude of tasks and domains that involve the characteristic processing features of MTL. Hippocampus supports relational representations, while perirhinal cortex supports item (i.e. fused, unitized or configural) representations (Cohen & Eichenbaum, 1993; Eichenbaum & Cohen, 2001). This characterization of MTL function anticipates the contribution of hippocampus to tasks that place sufficient demands on relational representations, regardless of delay, timescale, or domain. Experimental Chapters 3, 4, and 5 reveal contributions of MTL during on-line processing to domains of perception, language, and creativity.

The future of cognitive neuroscience is exciting. Advancements in sophisticated technologies are leading to new findings. More precise methods of measurements are available in studies of brain imaging, neuronal signaling, and neuropsychological lesions. Great researchers are contemplating new ideas about the contribution of individual brain regions and particular functional networks, operating in real-time. Even the growing amount of public interest makes this a very exciting time for the field. Hopefully, one day our understanding of the brain will lead to more effective treatments of neuropsychiatric and neuropsychological diseases. Advancements in this direction already appear promising. But I still find myself wondering about the nature of the human mind, simultaneously baffled and intrigued by its complexity. Is it true that …

"*If the brain were so simple we could understand it,*
we would be so simple we couldn't" - Lyall Watson

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