BEHAVIORAL AND NEURAL CORRELATES OF EPISODIC MEMORY REGULATION

by

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A Dissertation Submitted in
Partial Fulfillment of the
Requirements for the Degree of

Doctor of Philosophy
in Psychology

at

The University of Wisconsin-Milwaukee
August 2021

ABSTRACT

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The University of Wisconsin-Milwaukee, 2021
Under the Supervision of Professor Deborah E. Hannula

Episodic memory retrieval, while critical for daily living, needs to be regulated to maintain goal-directed behavior. Past work has shown that episodic memory regulation engages brain regions involved in cognitive control, such as the dorsolateral and ventrolateral prefrontal cortex. These regions interact with the medial temporal lobe structures to control retrieval processes. In the current study, I paired eye-tracking, a sensitive index of memory, with fMRI in a novel paradigm to address several open questions in the field of episodic memory regulation. Participants initially encoded three celebrity faces and three tools with multiple indoor and outdoor scenes. In a subsequent retrieval and search phase, participants were presented with scene cues and were instructed to either retrieve the associate of the scene, suppress it, or substitute it with one of the other encoded objects. After a delay, a search display consisting of the six encoded objects, intermixed with six dots was presented, and participants completed a simple visual search task with the dots. Incidental viewing directed to the associate of the scene cue was used as a measure of the success of episodic memory regulation. Results revealed that the two strategies of memory regulation tested here – retrieval suppression and thought substitution – led to a decrement in memory performance for pairs in which the associate was a tool. Memory regulation was also linked with reduced viewing of the associate embedded in the search display. Further, retrieval suppression and thought substitution activated distinct brain regions suggesting that although the two strategies have similar behavioral consequences, they are associated with distinct task demands. Finally, memory regulation affected the neural representation of retrieved memories in the hippocampus. However, the precise direction of this effect was different for faces and tools. Overall, the study yielded novel insights into the precise behavioral and neural substrates involved in two strategies of episodic memory regulation, and the effect of these processes on the representation of retrieved memories in the hippocampus.

To my grandmother, Mangala Aji,

for being one of my first female role models,

and my loudest cheerleader.

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ACC	Anterior Cingulate Cortex
ANOVA	Analysis of Variance
AOI	Area of Interest
BOLD	Blood-Oxygen Level Dependent
dlPFC	Dorsolateral Prefrontal Cortex
EPI	Echo-planar Imaging
ERP	Event-related Potential
fMRI	Functional Magnetic Resonance Imaging
FWHM	Full-Width at Half Max
IFG	Inferior Frontal Gyrus
IPL	Intraparietal Sulcus
ITI	Inter-Trial Interval
MCW	Medical College of Wisconsin
MNI	Montreal Neurological Institute
MTL	Medial Temporal Lobe
PFC	Prefrontal Cortex
PrC	Perirhinal Cortex
PTSD	Post-Traumatic Stress Disorder
ROI	Region of Interest
RSA	Representational Similarity Analysis
RT	Reaction Time
SPL	Superior Parietal Lobe

SD	Standard Deviation
SMA	Supplementary Motor Area
SFG	Superior Frontal Gyrus
TE	Echo Time
TNT	Think/No-Think
TR	Repetition Time
UWM	University of Wisconsin Milwaukee
vlPFC	Ventrolateral Prefrontal Cortex

ACKNOWLEDGMENTS

I would like to, first and foremost, thank my advisor, Debbie, for taking a chance on me and for entrusting me with so many interesting and challenging projects in the lab. I am always in awe of your ability to the get to the heart of any problem. I hope that I have imbibed some of your scientific integrity and rigor – even a fraction of it, I'm confident, will carry me through my academic career.

I would also like to thank the Department of Psychology staff. Dr. Lima, Anna, Pat, Nicole and Glenda – thank you for always supporting the graduate students in the department. We all owe an enormous debt of gratitude to you. This work would not have been possible without the incredibly helpful MRI techs at the Medical College of Wisconsin. Thank you to Tina, Amy, Marlys and both Steve's for all your help during scanning, and sorry for making you sit through such a long and tedious experiment!

To Jenna – you've been my friend, philosopher and guide, not just in science, but also in life. You were also the best quarantine buddy I could have asked for! I will be forever grateful for our countless conversations over coffees, wine and margaritas. Thank you also to my Milwaukee family, Carissa, Adam, Allie, Greta, Joshua, Laura and Shahd, for bringing so much light to the long and arduous journey, that is science. You all made Milwaukee feel like home. Special shoutout to all the ladies from CLAMs for being my badass-female-scientist role models!

I wouldn't be anywhere without the unwavering love and support from Aai, Baba and Sai. Thank you for always believing in me, even when I didn't believe in myself. Counterintuitive as it may seem, your constant reassurance that I could drop everything and come back home gave me the strength to persevere through the program. And last but not the least – thank you to Siddhant. You have been my pillar of strength. Thank you for always answering my 3am hysterical phone calls, for bringing me back from the brink of burnout more times than I can count, and for always being the voice of reason (and humor) in my life!

This work was supported by a National Science Foundation CAREER award 1349664 to DEH. Any opinions, findings, and conclusions or recommendations expressed in this material are those of the authors and do not necessarily reflect the views of the National Science Foundations.

Behavioral and Neural Correlates of Episodic Memory Regulation

Episodic memory retrieval is critical for daily living. However, not all memories are one's that are worth remembering. Oftentimes cues in the environment can trigger the retrieval of unpleasant or traumatic memories. In such situations, retrieval needs to be curbed or regulated to limit the awareness of such unwelcome memories. This is especially important in the context of mental health disorders such as post-traumatic stress disorder (PTSD) and depression that are associated with recurrent intrusion of unwanted memories (Schlagenhauf et al., 2021; Anderson & Huddleston, 2012). Two strategies of memory regulation have been investigated in the literature – the first one, retrieval suppression, involves pushing retrieved information out of awareness. The second investigated strategy of thought substitution entails calling to mind different information instead of the retrieved memory. Past work has shown that memory regulation can lead to long-term forgetting (Anderson & Green, 2001), reduced vividness of retrieved information (Meyer & Benoit, 2021), and decreased expression of the suppressed memory in later thought (Wang et al., 2015). This process, which involves top-down control of memory retrieval, is associated with increased brain activity in cognitive control regions, and decreased activity in regions involved in memory retrieval.

The current study was designed to build on this work and address three under-investigated questions in the field of memory regulation. First, I examined the neural correlates of thought substitution under conditions in which participants had some flexibility in terms of the information used for substitution. Second, I investigated brain regions involved in successful memory regulation using an online, incidental measure of regulation. Third, I examined effect of memory regulation on the neural representation of retrieved information. Past work has shown that eye-movements are sensitive to memory. In the current study, eye-tracking was paired with fMRI in a novel design developed to examine the behavioral and neural correlates retrieval suppression and thought substitution.

Episodic Memory and the Medial Temporal Lobe

Episodic memory refers to our long-term memory for events. These memories are rich in detail, and consist not only of the individual elements of an event, but also the relations between them. Hence, for successful episodic memory formation discrete elements of an event need to be bound together into a coherent whole (Konkel & Cohen, 2009). For instance, the memory of a friend's birthday party consists of a bound representation of the memory for people encountered at the party, the food served at the party, the spatial layout of the location of the party, and so on. This kind of memory for spatial, temporal and associative relationships between individual elements of an experience is termed relational memory.

It is widely accepted that relational memory depends on structures in the medial temporal lobe (MTL; Cohen & Eichenbaum, 1993). Of the MTL subregions, the hippocampus is especially critical for the binding of discrete elements of an experience into a single representation during encoding, as well as for the retrieval of these elements during test (Ranganath & Ritchey, 2012; Hannula et al., 2013; Ranganath, 2010; Hannula & Ranganath, 2009; Konkel & Cohen, 2009; Davachi, 2006; Tulving, 2002; Cohen & Eichenbaum, 1993). A particularly compelling demonstration of the involvement of the hippocampus in relational memory came from a neuropsychological study by Konkel et al. (2008). In their study, patients with hippocampal amnesia completed a task which tested item and relational memory using the same set of materials. Here, in an initial study phase, patients and age-matched controls were presented with sets of three objects that appeared sequentially in different spatial locations on the screen. In a subsequent test phase, participants' memory for individual items was tested. In addition, they were also tested on their memory for the associations between the objects in a set (associative relations), the objects and their spatial locations (spatial relations), or the order of presentation of objects in the study phase (temporal relations). They found that compared to age-matched controls, patients with damage that was largely limited to the hippocampus were disproportionately impaired at all tests measuring relational memory, whereas their memory for individual items was relatively spared. In contrast, patients with extensive medial temporal lobe lesions were impaired on tests of relational as well as item memory. Further evidence for the involvement of the hippocampus in relational memory comes from several fMRI studies that demonstrated that the hippocampus is selectively recruited during encoding (Prince et al., 2005; Davachi et al., 2003) and retrieval (Giovanello et al, 2009; Giovanello et al., 2004; Prince et al., 2005) for tasks involving relational memory (see Olsen et al., 2012; Konkel & Cohen, 2009; Cohen et al., 1999 for reviews).

Reinstatement of Information during Episodic Memory Retrieval

It has been suggested that the hippocampus supports memory retrieval through the reinstatement of encoded information (Norman & O'Reilly, 2003; McClelland et al., 1995). According to this account, the presentation of a contextual cue triggers pattern completion processes in the hippocampus and surrounding MTL areas. This, in turn, leads to the reactivation of encoded information in the hippocampus as well as other cortical areas that are involved in the processing of sensory information. As mentioned above, previous fMRI studies have found evidence for the involvement of the hippocampus in memory retrieval (Giovanello et al., 2009; 2004; Prince et al., 2005). However, in these studies hippocampal recruitment is measured simply as an *increase* in the activity of the hippocampus during a retrieval task. As a result, from this data no inferences can be made about whether specific representations are activated in this

this region to support retrieval. Recent advances in fMRI analyses, however, have permitted us to directly test the reinstatement hypothesis. These analysis techniques use multivariate approaches to capitalize on the distributed pattern of activity across the brain, allowing us to decode representational *content* from brain activity (Xue, 2018; Levy & Wagner, 2013; Kriegeskorte et al., 2008; Norman et al., 2006). In one such technique called Representational Similarity Analysis (RSA), a “representational template” corresponding to encoded information (e.g., each encoded object) or the encoding episode (e.g., elements experienced in the context of an encoding trial) is obtained for each individual participant (Dimsdale-Zucker & Ranganath, 2018). Reinstatement of the encoded object and/or context during retrieval is then quantified as the similarity (or correlation) between retrieval-related brain activity and the representational template of the object or encoding episode, respectively.

fMRI studies have employed this technique to measure reinstatement in the hippocampus during retrieval (Liang & Preston, 2017; Tompary et al., 2016; Wing et al., 2015; Staresina et al., 2012). Early studies showed this effect using encoding-retrieval similarity, where reinstatement is measured as the correlation in the pattern of activity in a specific brain region (e.g., the hippocampus) between encoding and retrieval episodes. In one such study, participants initially encoded several cue-associate pairs of pictures of objects (e.g., bottle-clover, teapot-clover, guitar-lobster, hammer-lobster), and subsequently attempted to retrieve the associates when presented with cues (Tompary et al., 2016). Critically, across pairs, trial-unique cue objects (e.g., a bottle, teapot, guitar, hammer, cookie etc.) were paired with the same 4 associates (a clover, a baby bottle, a lobster and scissors), permitting the comparison between associate-specific and episode-specific reinstatement at retrieval. During retrieval, cue objects were presented (e.g., bottle), and participants were asked to recall the associates (clover). Tompary et al. (2016) found that encoding-retrieval similarity in the hippocampus was greater between retrieval trials and the corresponding encoding trials (bottle-clover trial), as compared to other encoding trials involving the same associate (e.g., teapot-clover presentation during encoding). This suggests that retrieval involves the reinstatement of the *specific* episode of encoding, in addition to the general perceptual reinstatement of the encoded object (Dimsdale-Zucker et al., 2018; Tompary et al., 2016; Staresina et al., 2012).

Reinstatement has also been measured by comparing retrieval-related activity with activity patterns corresponding to associates obtained independently of the encoding trials (e.g., Mack & Preston, 2016; Wimber et al., 2015). These studies typically consist of a pre-exposure block, where participants are presented with objects that will subsequently be encoded as parts of pairs. Brain activity from this block is used to derive representational templates associated with each of the objects independent of the encoding episode. Reinstatement during a later retrieval task is measured as the correlation between the brain activity in the retrieval task and the representational template of the retrieved object. The advantage of this approach is that, in contrast to encoding-retrieval similarity, here the pre-exposure and retrieval displays do not share any perceptual information, since none of the materials from the pre-exposure phase are present during retrieval. Hence, pattern similarity in these studies can be better attributed to the reinstatement of an encoded memory representation. Using this method studies have found both category-specific (Mack & Preston, 2016) and item-specific (Mack & Preston, 2016; Wimber et al., 2015) reinstatement in the hippocampus. Further, across participants, the level of pattern similarity is correlated with speed (Mack & Preston, 2016) as well as mean accuracy (Tompary et al., 2016; Kuhl & Chun, 2014) of memory decisions suggesting that the strength of reinstatement in the hippocampus has behavioral consequences.

Regulation of Episodic Memories

Although the ability to retrieve past experiences is essential for daily living, it may not always be adaptive. We often have the experience where past memories intrude upon our awareness as we try to complete tasks (e.g., recalling an embarrassing memory of spilling coffee while ordering at a café, or recalling a past experience of being mugged in a park when taking a walk through the park). Previous work has demonstrated that information retrieved from long-term memory has the potential to capture attention and disrupt goal-directed behavior (Nickel et al., 2020). In such situations retrieved memories need to be regulated by cognitive control mechanisms to minimize their influence on behavior (Anderson & Huddleston, 2012). In fact, the inability to sufficiently control such retrieved memories is associated with mental-health disorders such as PTSD (Stramaccia et al., 2020; Catarino et al., 2015; Levy & Anderson, 2008) and depression (Göbel & Niessen, 2021; Zhang et al., 2016; Hertel & Gerstle, 2003).

Strategies Used in Episodic Memory Regulation

Past work has investigated two distinct strategies that can be engaged for the regulation of retrieved memories (Benoit & Anderson, 2012; Hertel & Calcaterra, 2005). First, retrieved memories may be actively *suppressed* (retrieval suppression), for instance, trying *not* to think of the negative experience of being mugged when walking through a park. Second, retrieved memories may be *substituted* with other thoughts following contextual cues (thought substitution), which might entail thinking of a pleasant picnic spent in the park instead of the experience of being mugged.

Retrieval suppression has been quite extensively studied using the Think/No-Think (TNT) paradigm (Anderson & Green, 2001). In this task, participants encode several cue-target word pairs (e.g., ordeal-roach) and are trained to recall the target word when the cue is presented.

In a subsequent TNT phase, participants are required to control the retrieval of targets on a subset of trials. Here, cue words (e.g., ordeal) are presented in either green or red. When the cue is green (think condition), participants are instructed to recall the target word (roach). However, when cues are red (no-think condition), participants are instructed to suppress the memory of the matching word by pushing it out of awareness. Since it is not possible to directly observe awareness, the success of suppression in the TNT phase is measured as the accuracy of recall of the cue-target word pairs in a final test phase. In this part of the experiment, participants are presented with cue words and are instructed to recall the targets. Typically, memory for pairs in the no-think condition is worse than those in the think condition (Noreen & MacLeod, 2013; Waldhauser et al., 2012; Anderson & Green, 2001; for a review see Anderson & Hanslmayr, 2014) suggesting that the act of suppression weakens the memory for the cue-target pair, making it harder to recall the target. Importantly, this effect, termed the total control effect, requires that participants suppress of the *act of retrieval*. Simply instructing participants to refrain from saying the target word aloud in the no-think condition without any instructions to constrain the retrieval process does not have the same effect on subsequent memory for the cue-target pair (Anderson & Green 2001). In some studies memory for targets in the recall phase is also tested using an independent probe test. Here participants are presented with a semantic category and the initial letter of the target word, and are instructed to recall the studied item that fits the semantic category (e.g., insect: r______; recall roach) to assess whether memory for the target word is also impaired when tested with novel probes. Interestingly, mirroring the results from cue-target recall, memory for targets tested with the independent probes is also worse for trials in the no-think condition as compared to the think condition (Murray et al., 2011; Bergström et al., 2009; Anderson & Green, 2001). This suggests that retrieval suppression may inhibit the memory for the target in a cue-independent manner, rather than simply weakening the memory for association between the cue and target (Wang et al., 2015; Anderson & Huddleston, 2012; Anderson & Green, 2001). In some studies, a subset of the encoded pairs is not used in the TNT phase at all, but is tested in the final memory phase. Memory for these pairs is used as a baseline to control for factors such as memory decay as a result of time passed between the study and test phase (Anderson & Huddleston, 2012). As compared to these baseline items, memory for pairs in the think condition is better, whereas memory for pairs in the no-think condition is worse (Noreen & MacLeod, 2013; Anderson & Green, 2001). Taken together, these results suggest that the intentional suppression of targets in the TNT phase causes forgetting of the targets over and above what is expected as a result of memory decay or passive forgetting.

In addition to retrieval suppression, a modified version of the TNT paradigm has been employed to investigate thought substitution, a second strategy of episodic memory regulation. In these experiments, participants study two lists of cue-target pairs. In both lists, the same cues are used, however they are paired with different targets (e.g., ordeal-roach and ordeal-goblet; Hertel & Calcaterra, 2005; Wimber et al., 2015). In the main TNT phase, in the think condition, as before, participants are presented with cues (e.g., ordeal) and are instructed to recall the targets of the cues from the first encoded list (e.g., roach). However, to study thought substitution, in the no-think condition, participants are instructed to substitute the memory for the target from the first list with target from the second list encoded with the same cue (e.g., goblet). Similar to studies on retrieval suppression, memory for the cue-target pairs from the first list (e.g., ordeal-roach) presented in the no-think condition is worse than memory for the baseline items in the final recall phase (Wimber et al., 2015; Racsmány et al., 2012; Hertel & McDaniel, 2010; Bergström et al., 2009; Joormann et al., 2009; Hertel & Calcaterra, 2005). In fact, in a subset of studies that directly compared retrieval suppression and thought substitution, memory for pairs in the substitute condition was even worse than pairs in the suppress condition (Joorman et al., 2009; Hotta & Kawaguchi, 2009; Hertel & Calcaterra, 2005) suggesting that thought substitution might be more effective in weakening the memory of the original cue-target pair.

Brain Regions Involved in Episodic Memory Regulation

It has been suggested that regulation of episodic memories involves top-down control of retrieval processes in the hippocampus in the way that response inhibition involves the regulation of motor processes (Bergström et al., 2013; Anderson & Green, 2001; Anderson, 2003). In line with this idea, fMRI studies using the TNT paradigm have demonstrated that retrieval suppression engages the dorsolateral prefrontal cortex (dlPFC), ventrolateral prefrontal cortex (vlPFC) and the anterior cingulate cortex (ACC; Castiglione et al., 2019; Benoit et al., 2015; Anderson et al., 2004). These regions overlap with the network involved in response inhibition (Anderson & Weaver, 2009; Simmonds et al., 2008; Menon et al., 2001; Liddle et al., 2001). In addition, retrieval suppression is associated with reduction of activity in the MTL regions including the hippocampus (Paz-Alonso et al., 2013; Benoit et al., 2015; Butler & James, 2010; Anderson et al., 2004). Crucially, PFC activity in this task is negatively correlated with hippocampal activation (Gagnepain et al., 2014; Paz-Alonso et al., 2013), and on a subject-by-subject basis, is predictive of accuracy in the final recall phase such that higher PFC recruitment is associated with worse memory (Benoit & Anderson, 2012; Depue et al., 2007). Taken together these results suggest that regions implicated in cognitive control support top-down suppression of retrieval processes in the hippocampus in a way that has behavioral consequences (Benoit et al., 2015; Benoit & Anderson, 2012; Anderson et al., 2004).

Although the process of thought substitution poses similar cognitive control demands to retrieval suppression, some evidence suggests that the two processes are neurally dissociable. First, electrophysiological studies have shown that retrieval suppression is associated with a reduction of centro-parietal positivity, an ERP (event-related potential) marker of conscious recollection (Wilding & Rugg, 1996; Friedman & Johnson, 2000), and this reduction is predictive of the memory decrement observed for suppressed items (Mecklinger & Jäger, 2009; Hanslmayr et al., 2009). Thought substitution, on the other hand, does not involve a similar reduction of centro-parietal positivity (Bergström et al., 2009). Furthermore, in fMRI studies thought substitution is associated with an *increase* in hippocampal activity (Wimber et al., 2015; Benoit & Anderson, 2012). It has been suggested that these effects reflect the demand of retrieving information to use for substitution (Anderson & Huddleston, 2012). Second, one fMRI study that directly compared retrieval suppression and thought substitution found that while retrieval suppression is associated with increased activity in the right dlPFC, thought substitution selectively recruits the left vlPFC (Benoit & Anderson, 2012). This anatomical dissociation suggests that these two types of episodic memory regulation might involve distinct cognitive processes. For instance, it has been suggested that retrieval suppression represents a special case of a general mechanism of inhibition. This hypothesis is supported by the finding that overlapping regions in the right PFC are recruited across multiple tasks involving inhibition (e.g., motor stopping, retrieval inhibition, emotion regulation; Banich & Depue, 2015; Anderson & Hanslmayr, 2014). In a recent study by Apšvalka et al. (2020), participants completed interleaved blocks of a response inhibition (go/no-go) and retrieval suppression (TNT) task. Apšvalka et al. (2020) found that these tasks were associated with increased activity in a right-lateralized network involving the right prefrontal and inferior parietal cortices. On the other hand, in the way that thought substitution is tested using the modified TNT paradigm described above, the left PFC involvement has been suggested to reflect the resolution of competition between distinct memory representations (Benoit & Anderson, 2012).

Open Questions in Episodic Memory Regulation

Although extant work on episodic memory regulation has shed light on the behavioral and neural bases of retrieval suppression and thought substitution, some open questions remain and were addressed in the current study. The first question has to do with the neural correlates of self-directed thought substitution, i.e., what brain regions are recruited when participants choose the memory they use for substitution? As mentioned previously, in the modified version of the TNT paradigm that is used to study thought substitution, participants encode each cue with 2 targets. Then, during the TNT phase in the substitution trials, participants are simply instructed to recall the second of the two targets that was studied with the cue. This design may not capture the realistic process of thought substitution for two reasons. First, in the real world we often *choose* the content for substitution when we attempt to replace retrieved information in our awareness (e.g., choosing to remember a picnic in the park rather than a late-night stroll when attempting to replace the memory of being mugged in the park). Second, as it stands, this task requires participants to resolve competition between two possible associates encoded with the cue, rather than self-generating a thought to use for substitution, a probable, but as yet unexperienced alternative. Hence, it is possible that the involvement of the vlPFC (Wimber et al., 2015; Benoit & Anderson, 2012) in thought substitution reflects the demand of the task to select one of two competing memories (Kuhl & Wagner, 2010; Nee & Jonides, 2009; Badre & Wagner, 2007), rather than the process of thought substitution *per se*. Hence, in order to identify structures involved specifically in thought substitution, participants may need to be instructed to self-generate a memory substitute, since this process still requires retrieval (as in previous studies) but is less likely to produce competition.

The second question is about the precise neural substrates of these two control processes – i.e., what are the neural correlates of *successful* memory regulation? There are large individual differences in people's ability to effectively regulate retrieved information, and this ability correlates with individual traits like repressive coping (Hertel & McDaniel, 2010), rumination (Grant et al., 2019; Fawcett et al., 2015) and depressive symptoms (Hertel & Gerstle, 2003). In most previous studies, the control effect in the final recognition phase (i.e., decrement in memory for pairs that were suppressed) is used as an index of the success of memory regulation during the TNT phase. Although after averaging across participants the control effect is demonstrable, the magnitude of this effect is variable (Anderson & Huddleston, 2012). Despite this variability, most studies have not used an online measure of the success of memory regulation. As a result, it is possible that previous studies on the neural basis of episodic memory regulation lose some sensitivity to detect subtle neural differences by averaging across trials in which participants were *supposed to* regulate their memories, without taking into account the relative *success* of doing so.

The small handful of studies that have attempted to investigate the processes involved in successful regulation have found differences in brain activity as a function of how much the memory of the target intruded upon participants' awareness on a trial-by-trial basis based on *subjective reports*. In a study by Benoit et al. (2015) participants were asked to report at the end of every trial in the TNT phase, how often they had thought about the target while the cue was in view. They found that dlPFC activity was greater for trials in which participants reported higher levels of intrusion of the target in the no-think condition. Additionally, connectivity between the dlPFC and the hippocampus was predictive of the intrusion of the target, such that with repeated suppression attempts, increased coupling of the dlPFC and hippocampus was associated with lower subjective reports of intrusion (Benoit et al., 2015; Levy & Anderson, 2012). These results suggest that brain activity is sensitive to the success of regulating memories. As such, accuracy in the post-test recognition phase may not be a sensitive measure of the idiosyncratic strategies that participants might be employing on a trial-by-trial basis in the TNT phase. Hence, to get a more comprehensive picture of the neural correlates of successful episodic memory regulation, we need a more sensitive, online measure of this process.

Finally, the third question concerns the reinstatement of encoded information, i.e., how does episodic memory regulation affect the representation of retrieved information in the brain? It has been suggested that the act of episodic memory regulation involves the top-down control of retrieval processes in the hippocampus by the PFC. As mentioned previously, some recent studies suggest that retrieval in the hippocampus involves the reinstatement of encoded information (Dimsdale-Zucker et al., 2018; Tompary et al., 2016; Mack & Preston, 2016). It is, however, unclear how the process of episodic memory regulation affects the representation of retrieved information in the hippocampus. There is some evidence to suggest that the act of retrieval suppression modifies the representation of retrieved objects in the brain. In a study by Detre et al. (2013) participants encoded words that were paired with either a scene or a face. Next, they completed a standard TNT block where they were presented with word cues and were instructed to either retrieve or suppress the matching scene or face of the word. Detre et al. (2013) found that in suppress trials, classifier evidence for decoding the category of the matching target (i.e., identifying whether the associate was a face or a scene) from brain activity in the inferotemporal visual cortex (fusiform gyrus and parahippocampal gyrus) was at chance. This suggests that retrieval suppression may cause the representation of the retrieved information to be dropped from regions involved in the visual processing of these objects. However, this study did not examine whether the same effect is also observed in the hippocampus.

To my knowledge, only one study has directly tested the effect of episodic memory regulation on hippocampal representation of retrieved information, in addition to probing sensory representations in the ventral visual cortex (Wimber et al., 2015). This study employed the modified version of the TNT paradigm described above. Briefly, participants encoded each cue word with two target pictures. The two targets came from two distinct categories out of a possible three categories (a face, a scene or an object). In the TNT phase, participants were presented with cues and were asked to retrieve the first target encoded with the cue. It was assumed that in order to minimize interference from the second associate, it would be suppressed in favor the first associate. Wimber et al. (2015) found that with repeated attempts to retrieve the first associate, the pattern of activity in the ventral visual cortex became more and more dissimilar to the representational template of the second associate. This increase in dissimilarity with the template of the second associate across repeated retrieval of the first associate was correlated with univariate activity in the vlPFC, and was predictive of forgetting on the subsequent recognition memory test. The same effect was not observed in the hippocampus. Patterns of activity in the hippocampus became more similar to the template of the first associate with repeated retrieval of this object. However, contrary to the ventral visual cortex, there was no reduction in pattern similarity with the representational template of the second associate in the hippocampus. Although this study is a compelling demonstration of the claim that cognitive control mechanisms are able to alter the representation of retrieved information in the brain during episodic memory regulation, it is subject to some limitations. Similar to the limitations of previous studies discussed above, this study did not have a trial-by-trial behavioral measure of the success of suppression of the second associate. Additionally, here participants were not explicitly asked to suppress their memory for the second associate. Rather, it was assumed that in order to resolve the competition from the second associate while retrieving the first, cognitive control mechanisms would be engaged to suppress the second associate. If this is not the case (Maxcey et al., 2019), then the observed reduction in pattern similarity for this item may be a result of the upregulation of the representation of the first associate rather than suppression of the second one. It is possible, then, that reduction of reinstatement in the hippocampus is only evident under explicit instruction to suppress the retrieved information.

Current Work

In the current study, I plan to address these open questions by combining fMRI with eye-tracking. Eye-movements have been shown to be a reliable index of memory (Hannula, 2018; Meister & Buffalo, 2016; Hannula et al., 2012; Hannula et al., 2010; Kumaran & Wagner, 2009). Evidence across several studies shows that viewing behavior is affected by memory for individual items (Ryan et al., 2000; Althoff et al., 1999), and memory for spatial (Ryan et al., 2000), temporal (Ryan & Vilate, 2009) and associative (Hannula et al., 2007; Hannula et al., 2012) relations between items.

In one task that has been used to demonstrate the effect of memory on eye-movements (Hannula et al., 2007), participants initially encode a series of scene-face pairs. During a subsequent test phase, participants are presented with a scene cue that is meant to initiate pattern completion processes and trigger the retrieval of the matching face of the scene. Next, a 3-face display consisting of the matching face along with two equally familiar faces is superimposed on top of the scene. Studies using this task have found that when the 3-face display is presented participants rapidly allocate disproportionate viewing to the matching face of the scene (Hannula et al., 2007). This effect emerges within 500-750ms of test display onset, and is robust to task instructions. In fact, it has been suggested that this eye-movement-based memory effect is obligatory (Ryan et al., 2007), since it emerges even when conscious recollection fails (Hannula & Ranganath, 2009), when scenes are presented subliminally (Nickel et al., 2015), when participants are asked to conceal their memory for the matching face (Mahoney et al., 2018), and when they are told to ignore the associates and look directly at specific search targets (Nickel et al., 2020).

Importantly for the purposes of this study, results also indicate that these eye-movement-based memory effects are sensitive to hippocampal functioning. Studies in patients with hippocampal amnesia (Hannula et al., 2007) and schizophrenia (Hannula et al., 2010; Williams et al., 2010) have shown that eye-movement-based memory effects (e.g., disproportionate viewing of retrieved items) are either completely absent (hippocampal amnesia) or significantly delayed and attenuated (schizophrenia) in patients as compared to healthy controls. Furthermore, hippocampal activity is predictive of the presence of the eye-movement-based relational memory effect in healthy young adults. In a study by Hannula and Ranganath (2009) participants performed the task described above while undergoing concurrent eye-tracking and fMRI. It was found that activity differences in the hippocampus during presentation of the scene cue predicted the memory-based viewing effect, even when participants' behavioral response was incorrect (i.e., they failed to identify the associate from the three alternatives in the test display). This suggests that eye-movement behavior is a sensitive, online index of retrieval processes that are supported by the hippocampus (Hannula & Ranganath, 2009; Pathman & Ghetti, 2016) and may be used as an indirect, online measure of memory representations retrieved by the hippocampus when cues are presented.

As mentioned previously, episodic memory regulation alters hippocampal processing. Hence, in the current study I capitalized on the link between viewing behavior and hippocampal activity, and used eye-movement behavior as an online, trial-by-trial index of episodic memory regulation. Participants first encoded a set of three faces and three tools with multiple scenes. In a subsequent memory regulation and search phase, participants were presented with scene cues along with an instruction to either retrieve the encoded associate, suppress it, or substitute that memory representation with one of the encoded objects from the other category (e.g., substitute the memory of a face with a specific tool, and vice versa). After a delay period, a search display was presented in which all six encoded objects (three faces and three tools) were presented intermixed with black dots. Participants performed a visual search task where they were instructed to fixate a specific target dot on each trial. Hence, the encoded objects in the display were irrelevant to the search task that participants were instructed to complete. Incidental viewing directed to those objects was, however, used as a trial-by-trial index of episodic memory retrieval and regulation. It was expected that in trials when participants attempted to retrieve the associate of the scene cue, viewing would be directed disproportionately to the matching object embedded in the search display. On the other hand, in trials where participants attempted to suppress memory for the associate, viewing would be distributed across all objects in the search display. Finally, in trials where participants substituted the memory of the matching object with one of the other encoded objects, disproportionate viewing would be directed to the object that the participant had selected, on that trial, to serve as the substitute.

The proportion of viewing dedicated to the matching object in the search display was used to back-sort trials as a function of successful episodic memory regulation. Additionally, in the thought substitution condition, viewing behavior was used to identify the object that participants had selected as the substitute on a given trial. This permitted us to examine whether the representation of the retrieved object is dropped from the hippocampus in favor of the object used for substitution, on a trial-by-trial basis. With respect to the fMRI data, it was expected that, similar to past studies (Benoit & Anderson, 2012), retrieval suppression and thought substitution would be associated with activity differences in the distinct subregions of the PFC. Further, additional brain activity associated with self-generation of the thought substitute may be observed. It was also expected that activity in regions involved in episodic memory control would be modulated by regulation success, as measured by eye-movement behavior. Finally, I expected that similar to the effects demonstrated in regions involved in sensory processing (Wimber et al., 2015; Detre et al., 2013), memory regulation would be associated with the downregulation of the representation of retrieved information in the hippocampus.

Method

Participants

Thirty right-handed students from the University of Wisconsin Milwaukee (UWM) with normal or corrected-to-normal vision took part in the experiment. Participants were compensated with payment and/or course credit. One participant did not complete all study procedures and was excluded from the analysis. Two additional participants were excluded because of unreliable eye-tracking data (see eye-tracking data analysis section), and one participant was excluded because more than 35% of the TRs were censored (see fMRI preprocessing section). Data from 26 participants was carried forward for analysis (Age: *M* = 24.04; *SD* = 3.82; Range: 18-31 years; 13 female). Study procedures were approved by the Institutional Review Board of the Medical College of Wisconsin (MCW).

Materials

Stimuli in the experiment included 237 colored, indoor and outdoor real-world scenes (e.g., a city street, café, auditorium; 800 x 600 pixels) and six colored objects (three celebrity faces: Barack Obama, Rupert Grint, and Bruno Mars; and three tools: hammer, screwdriver, and scissors). The categories of objects (faces and tools) were chosen to improve our ability to examine between-category differences in brain activity (i.e., faces vs. tools; Haxby, 2012; Norman et al., 2006). Additionally, the individual exemplars were chosen such that, in addition to being easily recognizable, they would be perceptually different from each other. This was done to improve our sensitivity to examine the similarity of brain activity patterns at the level of individual exemplars within a category. Scenes were taken from an existing database (cf. Hannula et al., 2007). Faces and objects were taken from the internet, edited using Adobe Photoshop (Berkeley, CA) to ensure uniform size, and were placed on a solid grey background to match the color of the background used in the experiment (CIE L*a*b*: L=62.46, a=0, b=0). Of the 237 scenes, 18 were used during the practice phase, and 219 were used in the main experiment (three scenes were used in the pre-exposure phase, and the remaining 216 scenes were paired with objects during the encoding phase).

Design and Procedure

Screening session

Prior to scanning, participants completed a screening session at UWM. At the beginning of this session, participants signed a consent form and were screened for MR contraindications and exclusion criteria that would preclude enrollment in the study. If participants were MR-safe and otherwise eligible to continue (they were right-handed, between the ages of 18 and 35, and had normal or corrected-to-normal vision), they were provided with instructions and completed a practice block of the hybrid encoding-and-test, and search phases of the main experiment (see below). Conducting practice prior to MRI scanning permitted me to ensure that participants understood the task and to determine whether reliable eye-tracking data could be collected. Only the subset of participants whose eyes could be reliably tracked were invited to MCW to participate in the fMRI experiment.

fMRI testing session

At MCW participants completed four phases: a pre-exposure phase, a hybrid encoding-and-test phase, a memory regulation and visual search phase, and a final recognition phase (Figure 1A). In order to limit the amount of time participants spent in the scanner, the hybrid encoding-and-test phase was conducted outside of the scanner, as was the final recognition test. This was meant to minimize head motion and discomfort that might be experienced by participants who are required to stay in the scanner for prolonged periods of time.

Pre-exposure phase (scanned)

The purpose of this phase was to obtain a "representational template" for each object, *before* it was paired with a scene. This template was used to measure re-activation of each object, following scene cues, during the search phase (see below). In the pre-exposure phase, participants were presented with three out of 219 scenes reserved for the main experiment, as well as the six objects that were subsequently paired with scenes in the encoding phase. Each trial began with the presentation of a face, a tool, or a scene for 1s. This was followed by a 3, 5, or 7 second jittered inter-trial interval (ITI) leading to an average trial duration of 6s. Participants performed a one-back task, i.e., they responded with a button-press while the stimulus was in view, if the picture in a given trial was an immediate repeat of the one seen in the preceding trial. This task was meant to encourage participants to actively attend to the stimuli when they were presented. Participants completed six blocks of the one-back task during the pre-exposure phase. In each block, the three faces, three tools and three scenes were each presented twice leading to a total of 18 trials per block. Each block had three "targets" (i.e., three immediate repeats), and across blocks each picture served as the target twice. The target trials (i.e., immediate repeats, when button presses were made) were dropped from analyses, resulting in 10 trials per object across runs. A T1-weighted image was acquired at the start of the pre-exposure phase. Each functional run lasted approximately 2 minutes (18 trials x 6s per trial = 108s + 8s of scan at the start and end of each run). Along with time required for participant setup, the pre-exposure phase lasted approximately 45 minutes.

Hybrid encoding-and-test phase (not scanned)

In this phase of the experiment, participants completed three interleaved blocks of the hybrid encoding-and-test procedure. Each block began with encoding. Participants were presented with a series of scene-object pairs and were instructed to commit them to memory. Each trial began with the presentation of a central fixation cross, followed by a scene (18.5 x 16.3 degrees of visual angle). The scene was in view for 1s after which an object from the set of 6 exemplars (three faces, three tools; 11.2 x 13 degrees of visual angle), was superimposed on top of the scene. In order to encourage deep encoding of the pairs, participants were asked to try and form associations between the scenes and objects (e.g., how likely are you find this person in this place; how might this tool be used in this setting?). The scene-object pair was in view for 4s. In each of the three blocks participants encoded 72 new scene-object pairs (each object was paired with 12 scenes in a block). In all, 216 pairs were seen (36 pairs per object) across all three of the encoding blocks.

Individual encoding blocks (i.e., 72 scene-object pairs), were immediately followed by a hybrid encoding-and-test procedure, which was used to ensure adequate learning. In each case, memory for the scene-object pairs that were presented in the preceding encoding block was tested, and participants had at least one more opportunity to encode each pair. Here, each trial began with an encoded scene, presented for 1s. The ensuing trial structure depended on the participant's response to this scene cue. If the participant could call to mind the object that had been paired with the scene during the encoding phase, they were instructed to make a button-press within 3s of scene cue offset. If this button press was made, a display containing all three encoded faces and all three encoded tools arranged in a horizontal line on the screen was presented after an additional delay of 1s. From this display, the participant selected the associate of the scene cue by making a corresponding button press (i.e., one for leftmost object, six for the rightmost object; see Figure 1C). In order to simplify search for the associate in the 6-object display, the objects were grouped by category (i.e., faces were presented on one side of the screen and tools were presented on the other side). However, to prevent participants from forming an association between specific objects and the response mapping, the position of the category on the side of the screen, and the order of the exemplars within the category was randomized on a trial-by-trial basis. Across trials the associate was roughly equally likely to appear in all six positions in the display. This display was in view until a response was made. Finally, and regardless of response accuracy, the trial ended with the presentation of the originally encoded scene-object pair (1s scene, 4s pair). Participants were instructed to use this opportunity to check their response. If, following the scene cue, the participant did *not* make a button press (indicating that they did not remember the associate), the scene-object pair was re-presented with the same timing parameters used in the initial encoding procedure. Memory for this pair was tested again later in the block. Upon re-test, the participant was not able to opt-out of recognition testing. They were forced to choose the matching object from the 6-object display. At the end of the trial, they were re-exposed to the correct scene-object pair after having made their choice, as above (see Figure 1C). This constraint ensured that participants got no more than two exposures to the scene-object pairs in the hybrid encoding-and-test procedure. In each hybrid encoding-and-test block, all 72 pairs that had been studied in the corresponding encoding block were tested (each object paired with 12 scenes). Across the three blocks, memory for 216 pairs was tested. Each encoding block lasted approximately 7 minutes, and each hybrid encoding-and-test block took between 20 and 25 minutes. Finally, before participants re-entered the scanner to complete the next phase of the experiment, they were given instructions about the search task. In all, this phase of the experiment took approximately 1.5 hours.

Search phase (scanned)

This was the main experimental phase of the session. Each search task trial began with a black central fixation cross presented for 500ms. Next, an instructional cue (the word “Retrieve”, “Suppress” or “Substitute”) was presented for 500ms at the center of the screen followed by an encoded scene, presented for 1s. The scene cue was followed by a delay period that lasted 7s, during which a grey fixation cross was presented. The instructional cue preceding the scene indicated to participants what they should do in response to the scene cue and during the delay period after the scene. For trials in the Retrieve condition, participants were instructed to call to mind, and actively maintain the associate of the scene cue throughout the delay period. In the Suppress condition, participants were simply asked to avoid thinking of the associate by pushing it out of awareness. Previous studies have shown that this instruction is sufficient to encourage participants to suppress the associate (e.g., Anderson & Green, 2001; Hertel & Calceterra, 2005; Benoit & Anderson, 2012). Finally, in the Substitute condition, participants were asked to call to mind a specific object from the opposite category of the associate (i.e., to call to mind one of the encoded tools when the associate was a face and vice versa).

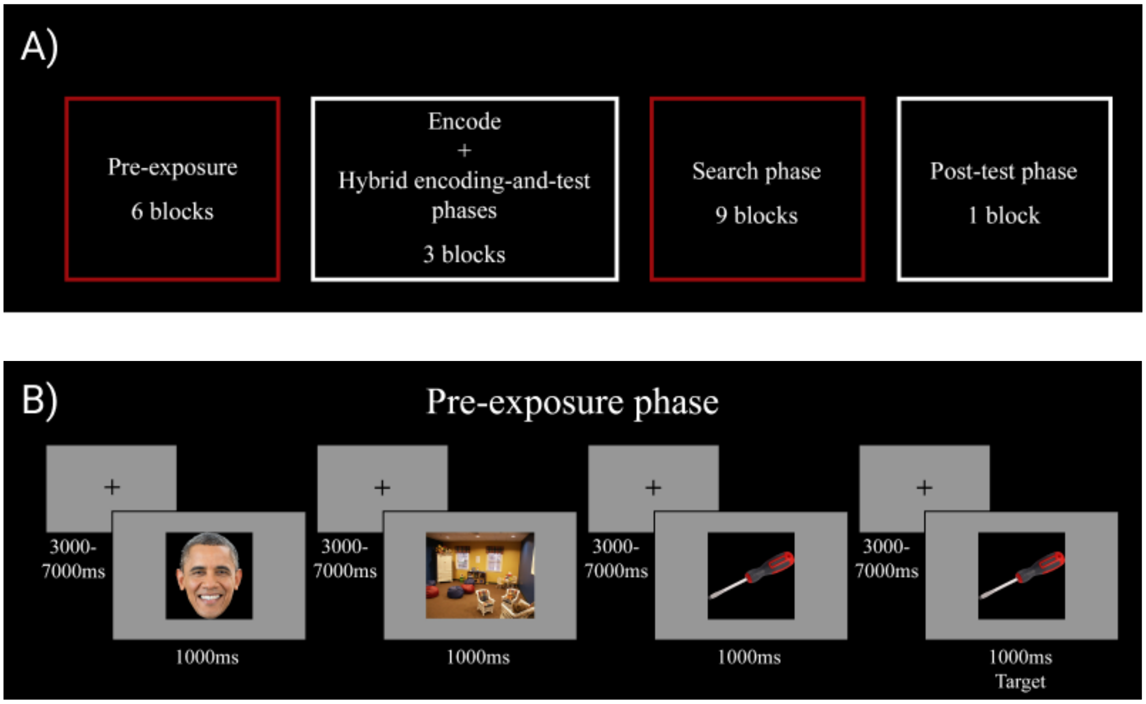
In the last 500ms of the delay, the fixation cross turned black to indicate to the participant that the next phase of the trial was about to begin. The delay period was followed by the presentation of a search display. The search display was an array of the six objects that participants had seen during encoding (three celebrity faces and three tools; 1.6 x 1.9 degrees of visual angle), interleaved with six black dots (0.8 x 0.8 degrees of visual angle), on the circumference of an imaginary circle centered on the fixation cross and superimposed on a uniform gray background (see Figure 1D). All of the objects were 11.4 degrees from the center of the screen and equidistant from each other. The positions of the faces and tools were randomly rearranged from one trial to the next, but the positions of the black dots remained the same. Participants were instructed to look at the elements in the search display freely. Three seconds after the search display was presented, all of the dots but one disappeared from the screen. This probe display remained in view for 1s and participants were instructed to make a single eye movement to the location of the remaining dot and to fixate it until the trial had ended. Importantly, all six objects were presented in the search display in every trial. However, the primary objective from the participants' perspective was to fixate the lone dot when the others were removed from view; no specific objective related to the objects themselves was discussed. Therefore, viewing patterns to objects in the search display served as an incidental index of memory retrieval and control. One possibility, tested here, is that viewing will be directed disproportionately to specific objects in the search display based on the preceding instructional manipulation – e.g., to the associate of the scene cue or, perhaps, an object from the opposite category (on substitute trials) – and provide information about what is being actively represented during the delay. Each trial ended with a 6/8/10s ITI (mean = 8s) during which a grey fixation cross was presented. In the last 500ms of the ITI, the fixation cross turned black to prepare participants for the next trial. The average total trial duration was 20s.

Participants completed 9 blocks of the search phase. Each of 9 blocks contained 18 trials (six trials each in the Retrieve, Suppress and Substitute conditions). Across blocks, 162 of 216 encoded pairs were used in the search phase (54 pairs per condition). Each run lasted approximately 7 minutes (18 trials x 20s per trial = 360s + 8 seconds at the start and end of each run). Along with the structural and localizer scans, this phase took 1.5 hours.

Post-test phase (not scanned)

Finally, in order to examine whether the top-down control of episodic memories weakened memory for the scene-object pairs (Anderson & Huddleston, 2012; Anderson & Green, 2003), in the last phase of the experiment participants completed a self-paced recognition memory test. Here, in each trial, a scene cue was presented for 1s. This was followed by a 6-object display similar to the one presented in the hybrid encoding-and-test phase (Figure 1E) from which participants chose the matching object. During this part of the experiment, memory for all of the pairs (162) used in the visual search task was tested, as well as the 54 encoded pairs that were not used in the search phase. These pairs provided a baseline measure of memory performance in the absence of attempted retrieval, suppression, or substitution in the search phase. Recognition accuracy and response times were examined for pairs used in the search phase to determine whether there was any memory enhancement for pairs in the Retrieve condition, and any memory decrement for pairs in the Suppress or Substitute conditions relative to items from the Baseline condition (Noreen & MacLeod, 2013; Anderson & Green, 2001; for a review see Anderson & Huddleston, 2012).

At the end of this phase, participants completed a short post-experimental questionnaire (see Appendix A). This questionnaire which is an extension of the one used in Hertel and Calcaterra (2005), was meant to assess any specific strategies that participants may have used in the Suppress and Substitute conditions, and to get information about whether participants were deliberately directing eye-movements to any specific objects in the search display. This phase lasted approximately 10 minutes.



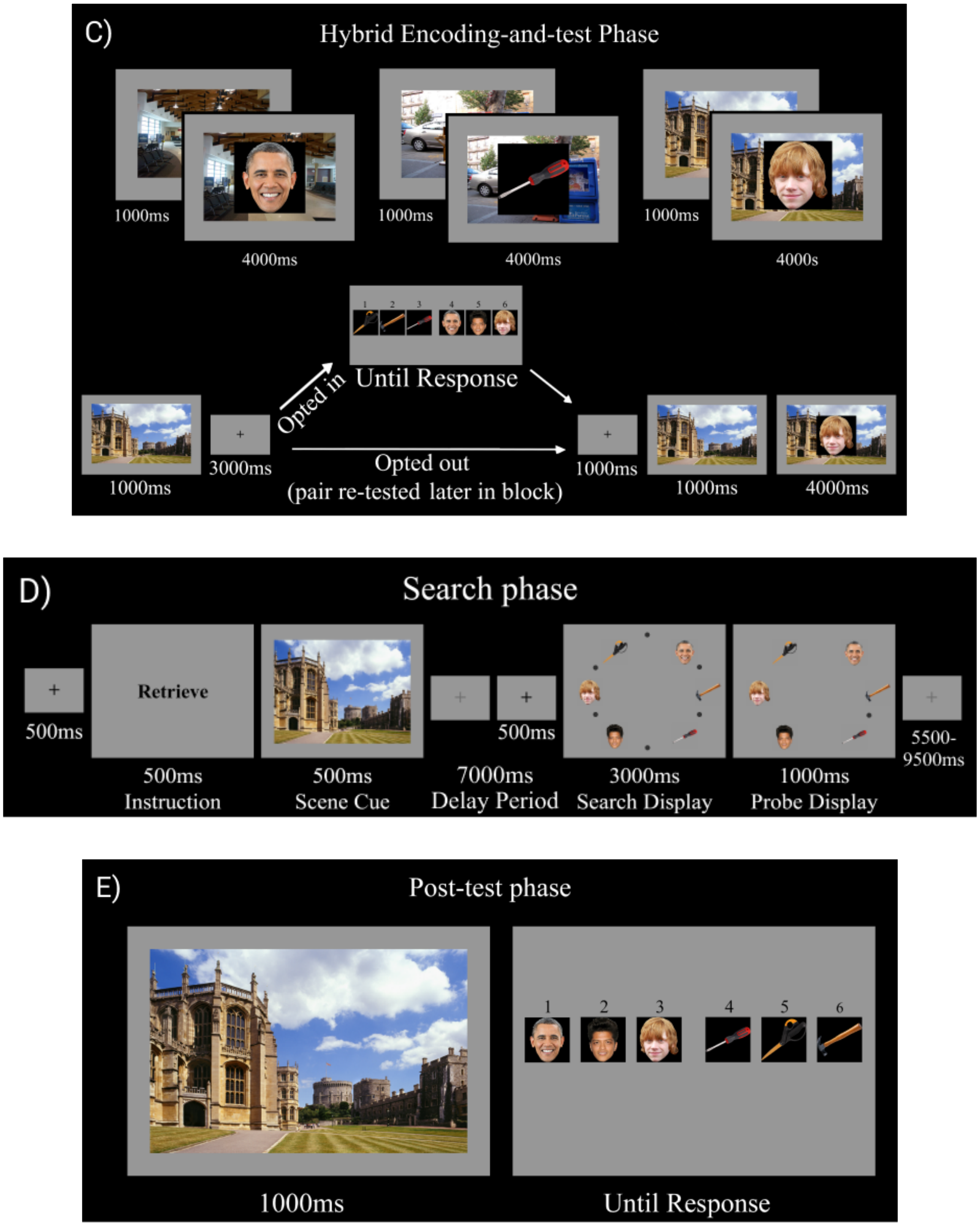


Figure 1. Overview of experimental procedure. **A)** Overview of experimental phases. Phases in red were completed in the fMRI scanner. **B)** Representative pre-exposure trials. **C)** Hybrid encoding-and-test phase. D**)** Illustration of single search trial. The last 500ms of the delay period was an alerting cue where the fixation cross turned black to prepare the participant for the search display. **E)** Representative trial in the post-test phase.

Counterbalancing

Two hundred and sixteen scenes were assigned to one of four lists (54 scenes per list). Each list contained equal numbers of indoor and outdoor scenes. Each object was randomly paired with nine scenes from each list (36 scenes in all). For a given participant, each list was assigned to one of four conditions (Retrieve, Suppress, Substitute, and Baseline). Across participants lists were rotated across conditions such that for instance, for participant 1, items from list A were tested in the Retrieve condition, list B in the Suppress condition, list C in the substitute condition, and list D in the Baseline condition. For participant 2, the lists were reassigned, so that items from list A were tested in the Suppress condition, list B in the Substitute condition, list C in the Baseline condition, and list D in the Retrieve condition. In this way, across participants, each list was assigned to every condition equally often. During the search phase, across blocks and conditions, the associate was roughly equally likely to appear in each of the six positions in the search display. Additionally, across blocks and conditions, the target dot was equally likely to appear in all six of the possible locations one, two, and three positions away from the associate. Finally, ITIs (6/8/10s) were randomly assigned to trials within a block with the constraint that trials from each condition were roughly equally likely to be paired with each of the three ITI durations.

Eye-tracking Apparatus

Eye position was recorded during fMRI scanning using an MRI-compatible Eyelink 1000 Plus Long-Range Mount eye-tracking system (SR Research LTD, Ontario, Canada). This system has a spatial resolution of 0.01°. Calibration was performed before the start of each run using a 9-point calibration procedure. Experiment Builder and Data Viewer (SR Research LTD, Ontario, Canada) were used to program the experiment and extract eye-tracking data, respectively.

fMRI Data Acquisition and Preprocessing

Scanning was performed at the Center for Imaging Research at MCW using a GE Healthcare Premier MR750 3T MR System (Milwaukee, WI) and a 48-channel GE head coil. Stimuli were presented on an LCD monitor positioned at the back of the scanner bore and viewed through a mirror mounted on the head coil. Padding was used to minimize head movements during scans. Both scanning phases (pre-exposure and search) began with a 3-plane localizer. Functional imaging data was acquired with a T2*-weighted multi-band gradient echo planar imaging (EPI) sequence (TR = 2s, TE = 23ms, Flip Angle = 77°, acceleration factor = 3; FOV = 24cm, image matrix = 120 x 120, in-plane resolution 2x2mm). Each volume included 75 sagittal slices, with a slice thickness of 2mm (no interslice gap), resulting in a voxel size of 2 x 2 x 2mm, with whole-brain coverage. Structural T1-weighted images were acquired using a spoiled gradient recalled (SPGR) acquisition sequence (TR = 8.1s, TE = 2.8ms, voxel size = $1mm^3$ isotropic, image matrix = 240 x 240, number of axial slices = 188).

Imaging data were preprocessed using AFNI (Cox, 1996) and Freesurfer (Fischl et al., 2002). Anatomical scans were skull-stripped and warped to a standard MNI template using a combination of linear and non-linear transforms in the @SSwarper wrapper script in AFNI. The T1 image was subject to automatic segmentation using Freesurfer. Standard preprocessing steps were used for the functional data. Pre-steady state scans (first four TRs; 8s) of each run were discarded (3dTcat). Data was then slice-time corrected (3dTshift) and motion-corrected by aligning all volumes of the session to the volume that contained the minimum number of outliers (3dvolreg). Volumes with over 0.3mm of frame-to-frame displacement, and volumes in which more than 5% of the voxels were outliers (signal intensity in each volume compared to the mean of the timeseries) were flagged for censoring in all univariate and multivariate analyses. One participant had 35% censored volumes in the search phase and was excluded from all analyses. In the remaining participants, on average 1.56% of volumes in the pre-exposure phase and 5.55% of volumes from the search phase were censored. Next, data was aligned to the T1 scan (align_epi_anat.py) using a linear alignment procedure. Finally, functional scans were warped to MNI space using the transforms from the T1 to MNI warp. In order to minimize smoothing by interpolation, the transforms from motion-correction, alignment and normalization were concatenated and applied to functional data in a single step (3dNWarpApply). Scans were visually inspected to ensure correct alignment of the native space EPI with the individual participant's T1 scan, as well as alignment of normalized EPI with the MNI template. Data were smoothed using a 4mm FWHM Gaussian kernel. The 3dBlurInMask tool was used for this purpose to ensure that data from non-brain voxels was not smoothed with brain voxels. Finally, the timeseries within each voxel was scaled to have a mean of 100 so that differences from baseline can be interpreted as percent signal change. Univariate analyses were performed on functional scans in MNI space. However, activity patterns for RSA were extracted from functional scans in participants' native space.

Data Analysis

Details of data analysis for each set of results are reported below. Generally, for all ANOVAs with more than one degree of freedom in the numerator, sphericity violations were tested using Mauchly's test. Where sphericity is violated, Greenhouse-Geisser adjusted degrees of freedom, p-values and epsilons are reported. For the behavioral and eye-tracking results, and for t-tests in the univariate region-of-interest analysis, post-hoc tests were corrected for multiple comparison using FDR correction, unless otherwise specified. Additionally, Cohen's *d* and partial eta-squared (η_p^2) values are reported as measures of effect size for t-tests and ANOVAs, respectively

Results

Hybrid Encode-and-test Phase

To ensure that there was no difference in learning between conditions prior to the search phase, data from the hybrid encode-and-test phase was examined using a repeated-measures ANOVA with the factors Condition (Retrieve, Suppress, Substitute, Baseline) and Associate Category (Face, Tool). During this phase of the experiment, participants had the option to opt-out of testing the first time a pair was presented. When participants opted-out, the scene-object pair was re-presented and memory for the pair was tested later in the block. First, I examined the percentage of total trials with opt-out responses on the first presentation. There was a main effect of associate category, $F(1, 25) = 27.65$, $p < 0.001$, $\eta_p^2 = 0.53$, but no main effect of Condition and no interaction between Associate Category and Condition, F's ≤ 1.02, p's ≥ 0.18, $\eta_p^2 \leq 0.06$. Pairs where the associate was a tool were repeated more often ($M = 20.73\%$, $SD = 19.72$, Range = 1.85 - 98.14) than pairs where the associate was a face ($M = 15.78\%$, $SD = 17.60$, Range = 0.93 - 99.07).

Accuracy in the hybrid encode-and-test phase was significantly above chance (i.e., 16.7% correct) for all conditions and associate categories, one-sample t's ≥ 22.08, p's < 0.001, d's $\geq$ 4.33. Similar to the percentage of repetitions, there was main effect of Associate Category on accuracy, $F(1, 25) = 45.61$, $p < 0.001$, $\eta_p^2 = 0.65$, but no main effect of Condition, and no Associate Category by Condition interaction, F's ≤ 1.92, p's ≥ 0.13, $\eta_p^2 \leq 0.07$. Accuracy was higher for pairs where the associate was a face ($M = 87.57$, $SD = 9.05$, Range = 60.94 - 100), as compared to pairs where the associate was a tool ($M = 78.17$, $SD = 11.62$, Range = 51.47 - 100).

Overall, these results suggest that there was no difference in learning between conditions before the search phase.

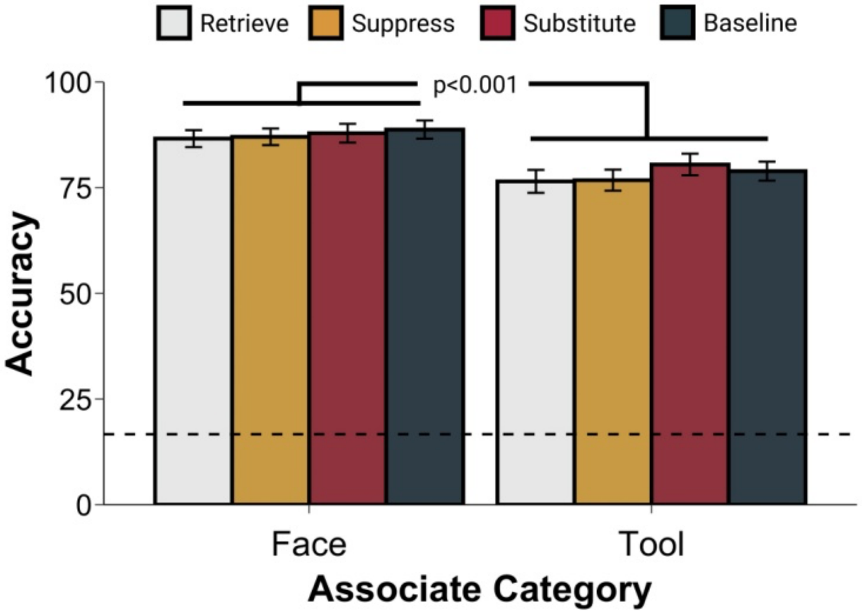


Figure 2. Mean accuracy in the hybrid encode-and-test procedure. Error bars represent SEM. Dashed line represents chance performance.

Post-test Recognition Phase

To examine the effects of retrieval, suppression, and substitution on memory for pairs, reaction time (RT) and accuracy in the post-test recognition phase were examined using repeated-measures ANOVAs with the factors Condition (Retrieve, Suppress, Substitute, Baseline) and Associate Category (Face, Tool). There were significant main effects of Associate Category, $F(1, 25) = 44.26$, $p < 0.001$, $\eta_p^2 = 0.64$, and Condition, $F(3, 75) = 5.09$, $p < 0.001$, $\eta_p^2 = 0.17$, in the RT data, but there was no significant interaction between Associate Category and Condition, $F(3, 75) = 1.31$, $p = 0.28$, $\eta_p^2 = 0.05$. Participants were slower at responding to tools ($M = 1312.44$, $SD = 625.36$) than faces ($M = 889.23$, $SD = 395.63$). The main effect of condition was driven by faster responses in the Retrieve condition as compared to the Substitute and

Baseline conditions, *t*'s ≥ 3.34, *p*'s < 0.01, *d*'s ≥ 0.20. No other pairwise differences were significant, *t* ≤ 2.60, *p*'s ≥ 0.09, *d*'s ≤ 0.19. (see Figure 3A).

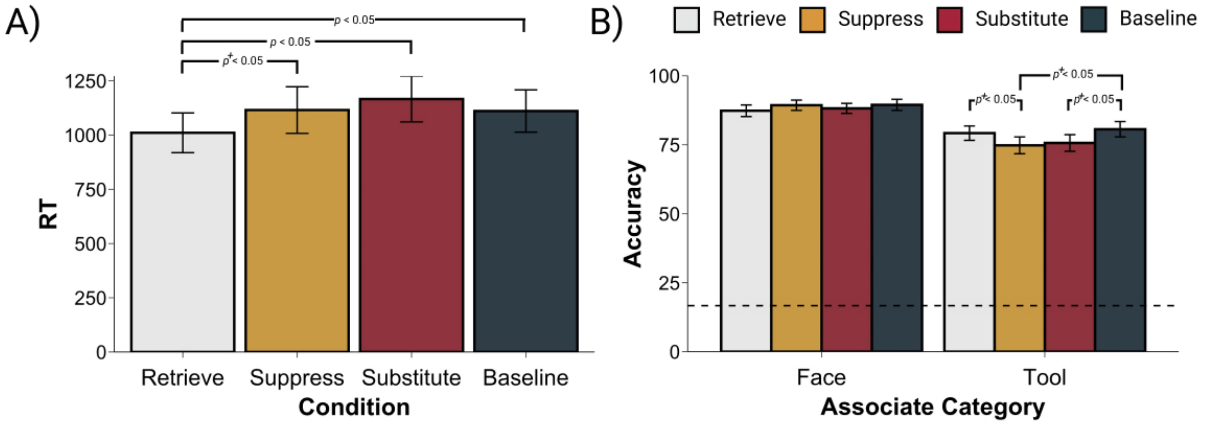


Figure 3. Performance in the post-test recognition phase. **A)** Mean reaction time and **B)** accuracy in the post-test recognition phase. Reaction time data is collapsed across faces and tools because there was no significant interaction between Condition and Associate Category. Error bars represent SEM. Dashed line represents chance performance. $^{+}$ uncorrected *p*.

Accuracy in the post-test recognition phase was above chance for all conditions and associate categories, *t*'s ≥ 19.07, *p*'s < .001, *d*'s ≥ 4.33. There was a significant main effect of Associate Category, $F(1, 25) = 80.77$, $p < 0.001$, $\eta_p^2 = 0.76$. The main effect of Condition, $F(3, 75) = 2.25$, $p = 0.09$, $\eta_p^2 = 0.08$, and the interaction between Associate Category and Condition were trending, $F(3, 75) = 2.33$, $p = 0.08$, $\eta_p^2 = 0.09$. Uncorrected pairwise post-hoc comparisons indicated that the interaction was driven by lower accuracy in the Suppress relative to the Retrieve, $t(25) = 2.25$, $p = 0.03$, $d = 0.30$, and Baseline conditions, $t(25) = 3.10$, $p = 0.004$, $d = 0.39$, for tools. Additionally, accuracy was lower in the Substitute relative to the Baseline condition, $t(25) = 2.15$, $p = 0.04$, $d = 0.34$, for tools. No pairwise differences between conditions were significant for faces, *t*'s ≤ 1.40, *p*'s ≥ 0.17, *d*'s ≤ 0.20 (see Figure 3B). Data from the post-test recognition phase suggest that regulating associates of the scene cues during the search phase induced forgetting in the post-test recognition phase when associates were tools but not faces. Furthermore, for both faces as well as tools, participants were faster to respond in the Retrieve condition, relative to all other conditions.

Memory Regulation and Search Phase

During the memory regulation and search phase, participants were presented with scene cues following an instruction to either retrieve the matching object of the scene, suppress it, or substitute the matching object with a specific object from the opposite category as the associate. Following a delay period, participants were presented with a search display consisting of the six encoded objects. However, these objects were irrelevant to the search task that participants were instructed to perform. Incidental viewing directed to these objects during the 3s search display was used an index of retrieval or regulation of the associate of the scene cue. First, trials in which less than 65% of eye-tracking data was available were discarded. Two participants, for whom more than 60% of the trials were flagged as bad, were excluded from all behavioral, eye-tracking and fMRI analyses. For the remaining participants, on average 20.75% of trials were excluded for unreliable eye-tracking data ($SD = 17.19$, Range = 1.23% - 50%). The percentage of trials excluded did not differ by Condition, $F(1.50, 37.50) = 0.31$, $p = 0.67$, $\eta_p^2 = 0.01$, $G\text{-}G\varepsilon = 0.75$, or Associate Category, $F(1, 25) = 0.86$, $p = 0.36$, $\eta_p^2 = 0.03$, and there was no interaction between Condition and Associate Category, $F(2, 50) = 2.17$, $p = 0.13$, $\eta_p^2 = 0.08$.

Proportion of Total Viewing.

To examine the effect of memory retrieval and regulation on eye-movement behavior, the search display was divided into eight Areas of Interest (AOI); six AOIs corresponding to the objects in the search display, one center AOI, and one AOI corresponding to the background, including the dots in the search display (see Figure 4A). The proportion of total viewing spent on each object was calculated by dividing the viewing time (in milliseconds) directed to the object by the total viewing time directed to the entire display. The effects of retrieval, suppression, and substitution on proportion of total viewing directed to the associate of the scene cue were tested using a repeated measures ANOVA with the factors Condition (Retrieve, Suppress, Substitute) and Associate Category (Face, Tool). There was a significant main effect of Associate Category on associate viewing, $F(1, 25) = 18.80$, $p < 0.001$, $\eta_p^2 = 0.43$, as well as a main effect of Condition, $F(1.05, 26.23) = 29.25$, $p < 0.001$, $\eta_p^2 = 0.54$, $G\text{-}G\varepsilon = 0.52$. The interaction between Associate Category and Condition was not significant, $F(1.23, 30.81) = 2.55$, $p = 0.11$, $\eta_p^2 = 0.09$, $G\text{-}G\varepsilon = 0.62$ (see Figure 4B). Associate viewing in trials where the associate was a face ($M = 0.15$, $SD = 0.07$) was higher than trials where the associate was a tool ($M = 0.11$, $SD = 0.05$). Regardless of the associate category, associate viewing was highest in the Retrieve ($M = 0.23$, $SD = 0.14$), relative to the Suppress ($M = 0.09$, $SD = 0.04$) and Substitute conditions ($M = 0.08$, $SD = 0.04$), t's ≥ 5.37, p's < 0.001, d's ≥ 1.27. There was no difference in associate viewing between the Suppress and Substitute conditions, $t(25) = 1.36$, $p = 0.55$, $d = 0.20$.

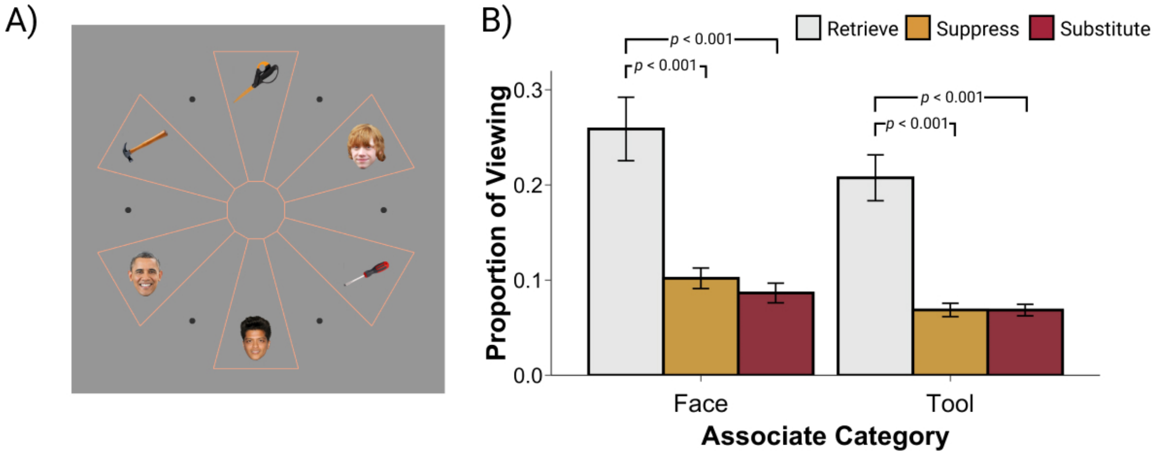


Figure 4. Proportion of total viewing **A)** Areas of interest used for the search display. **B)** Proportion of viewing dedicated to the associate embedded in the search display. Error bars represent SEM.

Object Prioritization

In addition to measuring the level of associate viewing, I was interested in how viewing-based prioritization changed as a function of retrieval and regulation on a trial-by-trial basis. For this purpose, a prioritized object was identified on each trial as the object in the search display that garnered the highest amount of viewing. I then calculated the proportion of trials on which this prioritized object was the associate, and the proportion of trials on which it was an object from the opposite category as the associate. ANOVAs were calculated separately for faces and for tools with the factors Condition (Retrieve, Suppress, Substitute) and Object Type (Associate, Opposite Category). Results revealed that for both faces and tools, the main effects of Condition and Object Type, as well as the interaction between Condition and Object Type were significant, F's ≥ 4.39, p's ≤ 0.01, $\eta_p^2 \geq 0.15$. Post-hoc t-tests indicated that for both faces and tools, the associate was the prioritized object more often in the Retrieve condition than the Suppress and Substitute conditions, t's ≥ 5.50, p's ≤ 0.001, d's ≤ 1.59. Additionally, the associate was more often prioritized in the Suppress relative to the Substitute condition, but only when the associate was a face, $t(25) = 3.02$, $p < 0.01$, $d = 0.56$. On the other hand, an object from the opposite category was more often prioritized in the Substitute and the Suppress conditions, relative to the Retrieve condition for both faces and tools, t's ≤ 4.00, p's ≤ 0.001, d's ≥ 1.17 (see Figures 5A and 5B).

Contrary to our expectation and participants' instruction, I found that an object from the opposite category was prioritized more often even in the Suppress relative to the Retrieve condition. However, it is possible that even though an opposite category object was prioritized in the Suppress condition, the proportion of total viewing time directed to that object was lower than in the Substitute condition, where participants were explicitly instructed to call to mind a specific object from the opposite category. To test this possibility, I repeated the above analyses – repeated-measures ANOVA with factors Condition (Retrieve, Suppress, Substitute) and Object Type (Associate, Opposite Category) conducted separately for faces and tools – on the proportion of total viewing time dedicated to the prioritized objects. For both faces and tools the main effects of Condition, and the Condition by Object Type interactions were significant, F's $\geq$ 4.22, p's < 0.05, $\eta_p^2 \geq 0.17$. The main effects for Object Type for faces and tools were trending, F's ≥ 3.65, p's ≤ 0.07, $\eta_p^2 \geq 0.15$. Post-hoc tests revealed that the proportion of viewing to the associate in trials where the associate was prioritized was highest in the Retrieve relative to the Suppress and Substitute conditions, t's ≤ 3.45, p's < 0.001, d's ≥ 0.53. For trials where an opposite category object was prioritized, viewing directed to this object was higher in the Substitute relative to the Retrieve condition, but only for tools. Additionally, consistent with expectations, even when an opposite category object was the most viewed object in the display, time spent viewing this object was significantly lower in Suppress than the Substitute condition for both faces and tools, t's ≥ 2.34, p's ≤ 0.05, d's ≥ 0.31 (see Figures 5C and 5D).

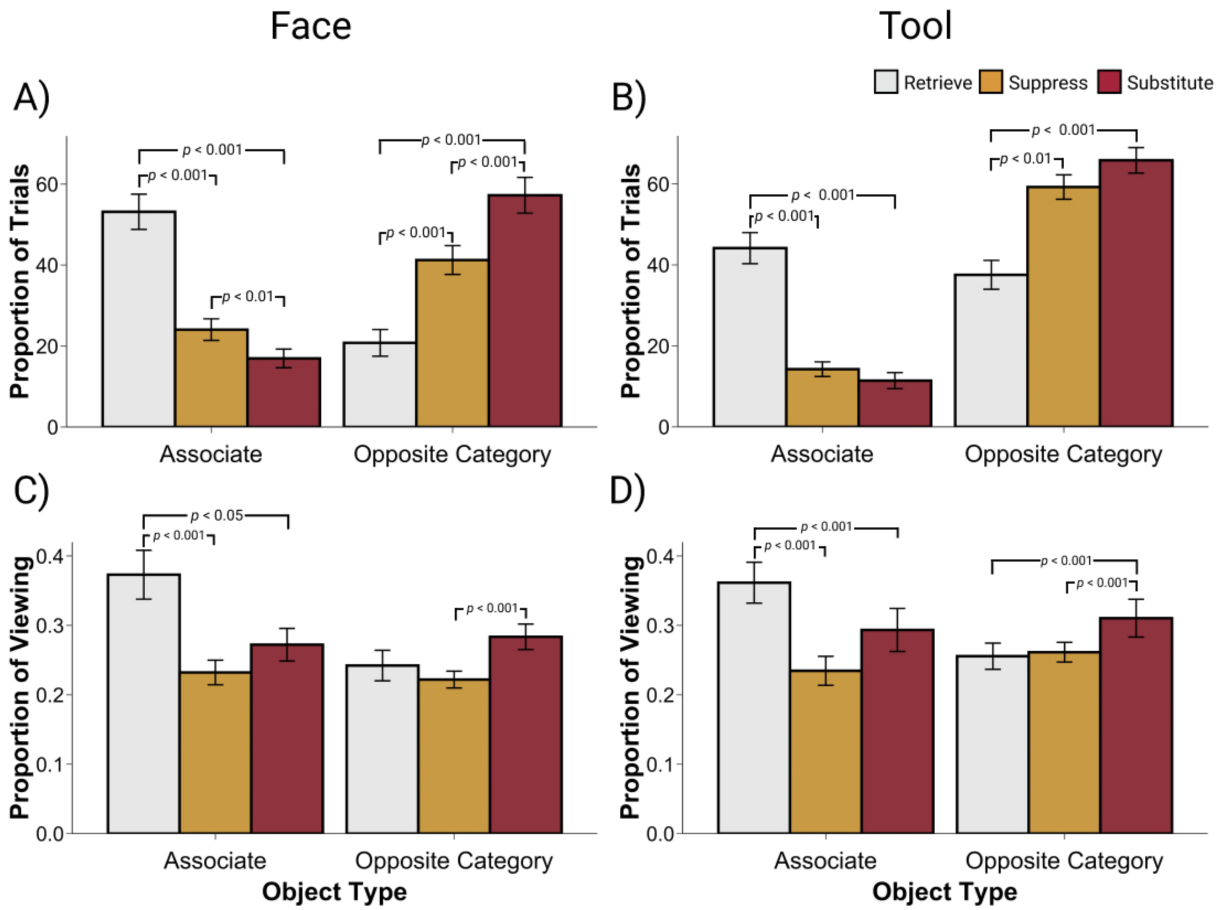


Figure 5. Viewing-based prioritization. Proportion of trials in which the associate or an object from the opposite category was prioritized for **A)** faces and **B)** tools. Proportion of viewing dedicated to the prioritized object when it was the associate or an object from the opposite category for **C)** faces and **D)** tools. Error bars represent SEM.

Taken together, these results suggest that eye-movement behavior is affected by memory regulation. The proportion of total viewing time directed to the associate of the scene cue was reduced in both regulation conditions relative to the Retrieve condition, and the associate was prioritized most often in the Retrieve condition. On the other hand, in both the Suppress and Substitute conditions, an object from the opposite category as the associate was prioritized most often. Importantly though, the proportion of total viewing time directed to this opposite category prioritized object was higher in the Substitute relative to the Suppress condition.

Question 1: Neural Correlates of Self-Directed Thought Substitution

The first goal of the current study was to examine the network involved in self-directed thought substitution. For this purpose, concatenated search runs were subject to a GLM (Friston et al., 1995). Each participant's regression matrix was generated in 3dDeconvolve with the onset of the following events modelled separately for each condition using the BLOCK4 function: The Scene cue period modelled from the onset of the Instruction cue (duration: 1500ms), the middle of the delay period (duration: 4000ms), and the onset of the search display (4000ms). Since the onsets of the instruction, scene cue and delay period occurred in quick succession in the trial, and necessarily followed each other with short, constant inter-stimulus intervals (~500ms) I combined the instruction and scene cue into one event, and modelled the middle of the delay period instead of the onset to have enough statistical power to deconvolve the unique contributions of the different events to the BOLD signal (Liu, 2012; Birn et al., 2002). Hence, the model constructed for this aim consisted of nine regressors (one regressor each for the combined instruction and scene cue (henceforth referred to as scene cue), the middle of the delay period (henceforth referred to as delay), and the search display, separately for the Retrieve, Suppress and Substitute conditions). Additional regressors modelling linear drifts and six demeaned head-motion parameters and their derivatives were included as regressors of no interest. Regression matrices generated through 3dDeconvolve were then used in 3dREMLfit to perform generalized least squares regression. This program estimates the temporal autocorrelation in the timeseries, and provides more stable, less biased t-values of the beta weights that can be used to examine group-level whole brain differences in activation between conditions.

First, I assessed whether regulation-related activity differences following the scene cue were evident in regions of the PFC and parietal cortex that have been implicated in direct suppression and thought substitution reported in past work using the TNT task. Additionally, to examine whether, similar to past studies, retrieval suppression was associated with reduced activity in the hippocampus (Anderson et al., 2004; Benoit & Anderson, 2012), activity differences were also extracted from an anatomical mask of the hippocampus derived from the Glasser et al. (2008) atlas (see Figure 6 for ROI locations). In the TNT task, participants are only presented with a memory cue in each trial of the TNT phase. Hence, scene-cue related activity was examined here because this trial period was most similar to past TNT studies. Contrast estimates from the Suppress > Retrieve and Substitute > Retrieve contrasts maps were extracted from a 5mm sphere centered around MNI coordinates reported in two previous studies (Apšvalka et al., 2020 and Benoit & Anderson, 2012), as well as from the anatomical hippocampal ROI. Here, a positive value indicates that activity was higher in the Suppress or the Substitute condition relative to the Retrieve condition. To test whether activity differences were significantly increased when participants were required to suppress or substitute previously encoded associates, a priori post-hoc tests were conducted using a one-sample t-test comparing these estimates from the Suppress > Retrieve and Substitute > Retrieve contrasts against 0. Additionally, to test whether activity in these ROIs was different across regulation strategies, contrast estimates for the Suppress and Substitute conditions were compared using a paired-samples t-test.

In four Regions of Interest (ROIs) derived from Apšvalka et al. (2020), namely the dlPFC, vlPFC, Supplementary Motor Area (SMA), and Inferior Parietal Lobe (IPL) in the right hemisphere, activity was significantly higher in the Suppress relative to the Retrieve condition,

t's ≥ 3.39, p's < 0.001, d's ≥ 0.67. Activity differences were also evident for the Substitute condition in the right IPL, $t(25) = 3.88$, $p < 0.001$, $d = 0.76$, but not the PFC ROIs, t's ≤ 0.98, p's ≥ 0.34, d's ≤ 0.19 (see Figure 7A). The difference between the Suppress and Substitute conditions was also significant in these ROIs, t's ≥ 2.08, p's ≤ 0.05, such that activity in the Suppress condition was greater than the Substitute condition. These results are consistent with the findings in Apšvalka et al. (2020), since these regions were reported to be part of a network involved in domain-general inhibitory control required for stopping retrieval (TNT task) as well as action (go/no-go task). I also tested whether the dissociation reported by Benoit and Anderson (2012) between the right and left PFC supporting suppression and substitution, respectively, was evident in the current study. Consistent with this work, in the right dlPFC, activity was significantly higher only in the Suppress relative to the Retrieve condition, $t(25) = 2.99$, $p < 0.01$, $d = 0.59$, whereas in the left vlPFC, there was a trend towards higher activity in the Substitute relative to the Retrieve condition, $t(25) = 1.85$, uncorrected $p = 0.07$, $d = 0.36$ (see Figure 7B). Activity in the right dlPFC was marginally higher in the Suppress relative to the Substitute condition, $t(25) = 1.90$, $p = 0.07$, $d = 0.43$. There was no difference between conditions in the left vlPFC, $t(25) = 0.63$, $p = 0.53$, $d = 0.09$. In the right and left hippocampus, contrasts estimates were not significantly different from 0, t's ≤ 0.74, p's ≥ 0.46, d's ≤ 0.15, and did not differ between conditions, t's ≤ 0.36, p's ≥ 0.72, d's ≤ 0.08.

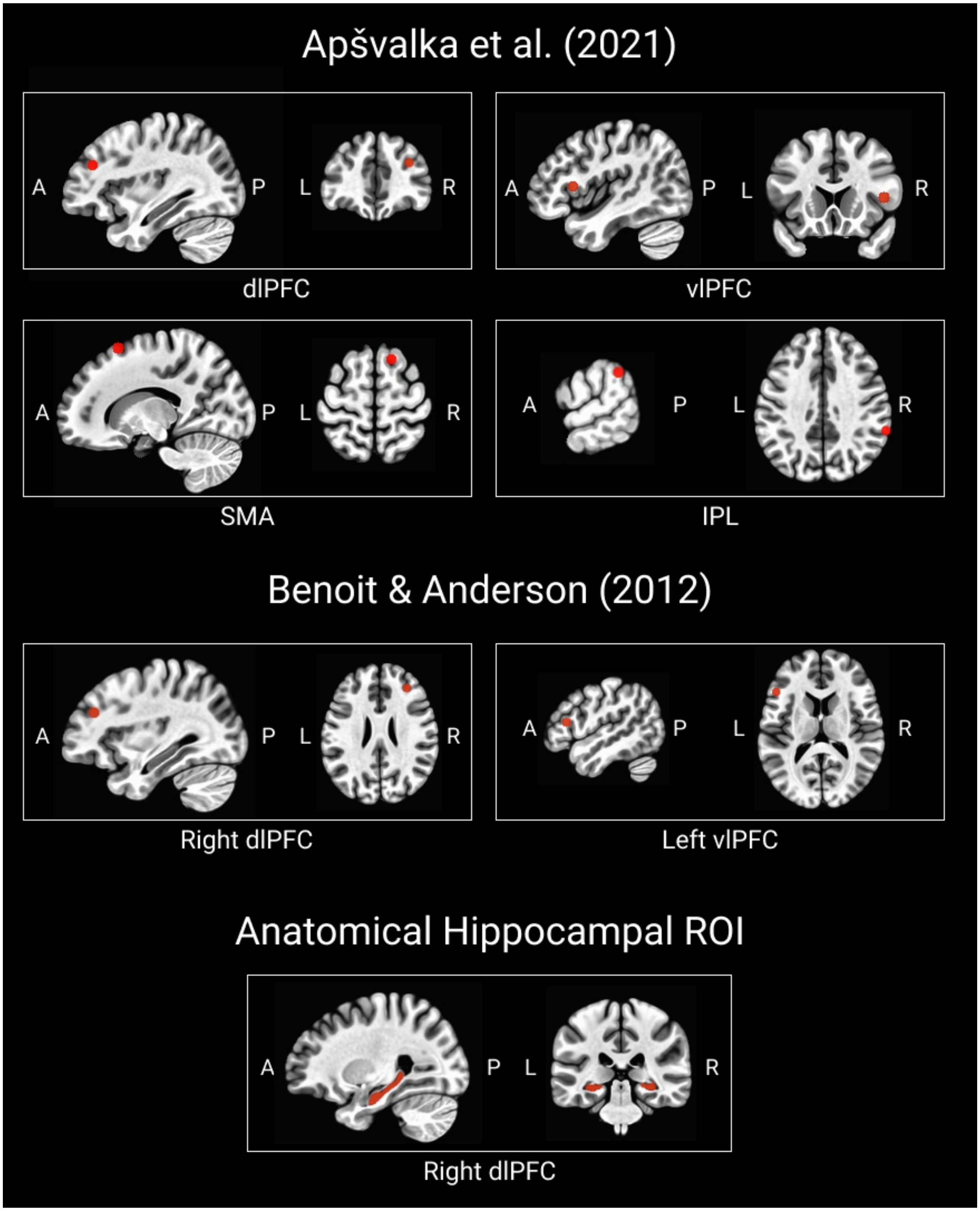


Figure 6. A priori Regions of Interest. Prefrontal and parietal ROIs from past papers that have used the TNT task, along with anatomical masks of the hippocampus.

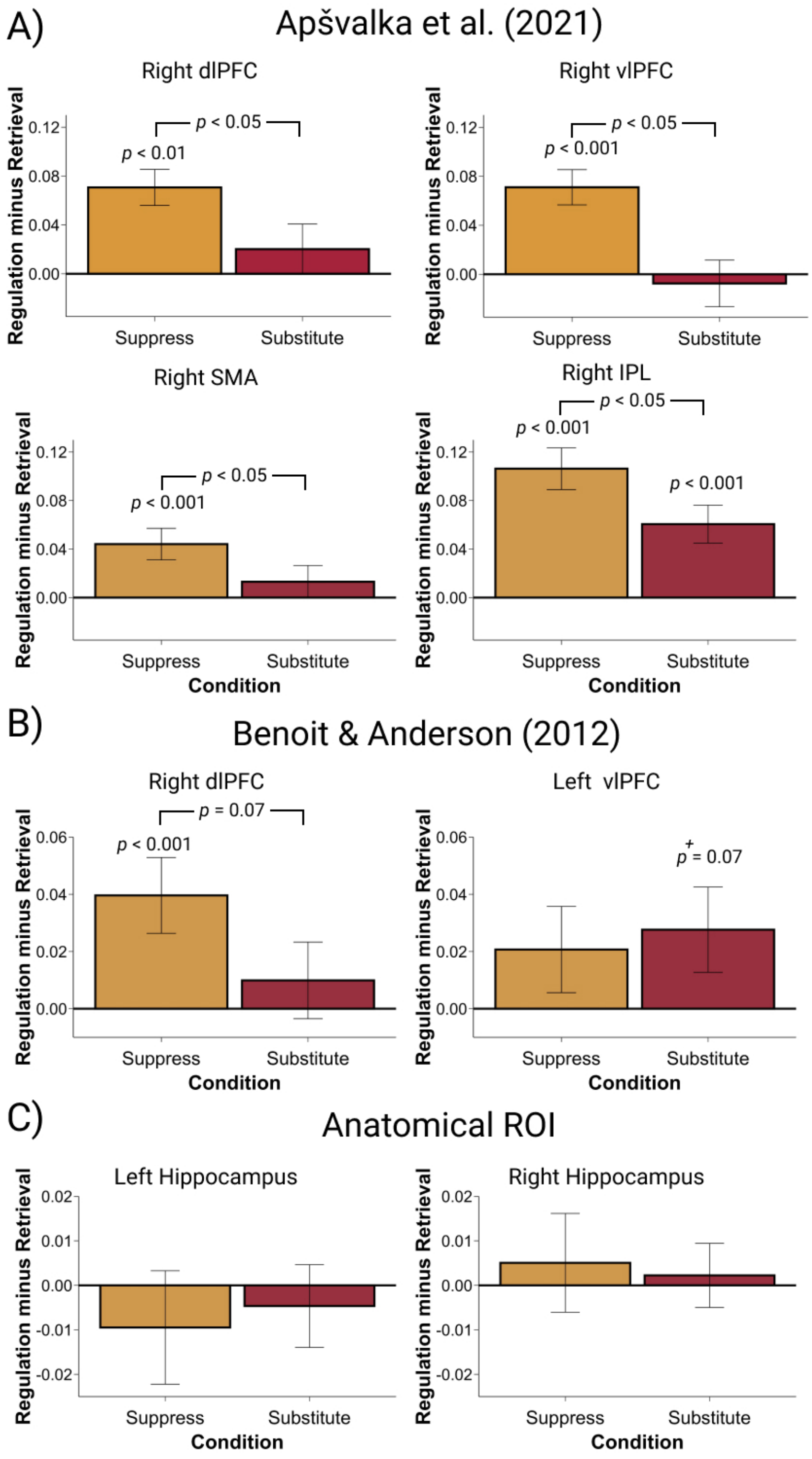


Figure 7. Univariate ROI data. Activity differences in Suppress and Substitute conditions relative to the Retrieve condition within a priori frontal and parietal ROIs derived from **A)** Apšvalka et al. (2020) and **B)** Benoit & Anderson (2012), and from the **C)** anatomical hippocampal mask. Error bars represent SEM. $^+$ uncorrected *p*.

In addition to probing these a priori ROIs, I also performed exploratory whole-brain analyses to examine suppression- and substitution-related activity in regions outside these ROIs. Suppress > Retrieve and Substitute > Retrieve contrast maps from the scene cue as well as the delay period were subject to a one-sample t-test using 3dMEMA (Chen et al., 2012). Statistical maps were thresholded at a voxel-wise threshold of $p < 0.01$ and a cluster threshold of $p < 0.05$. This corresponded to a cluster extent of 40 voxels as determined using Monte-Carlo simulations in 3dClustSim.

Activity differences during presentation of the scene cue, greater for both the Suppress and Substitute conditions than for the Retrieve condition, were evident in a distributed network including the dorsal and ventral PFC, intraparietal sulcus, superior parietal lobule, and the superior temporal sulcus/angular gyrus. Additionally, scene cue activity was greater in the Retrieve relative to both regulation conditions in the middle cingulate cortex and the thalamus (see Tables 1, 2, 3 and 4 for a list of significant clusters from the scene cue period).

Table 1. Clusters where activity was significantly higher in the Suppress than the Retrieve condition during the scene cue. Voxel wise threshold of $p < 0.01$, cluster threshold of $p < 0.05$.

Region	Hemisphere	Voxels	Peak Voxel (MNI)		
			x	y	z
Supramarginal Gyrus	Right	916	-67	37	41
Supramarginal Gyrus	Left	319	67	45	37
	Right	628	-17	-53	33
Middle Frontal Gyrus	Left	200	35	-55	27
(BA 46)	Left	175	41	-27	37
	Left	63	43	-41	35
Superior Frontal Gyrus	Midline	671	-13	-17	61
(BA 9)	Midline	46	7	-29	63
Inferior Frontal Gyrus (BA 44)	Right	383	-55	-29	-9
Inferior Frontal Gyrus (BA 44)	Left	180	53	-23	-7
Middle Temporal Gyrus	Right	63	-53	31	-1
Middle Temporal Gyrus	Left	53	57	29	-1
Fusiform Gyrus	Right	46	-19	67	-13
Orbitofrontal Cortex	Right	42	-49	-51	-5

Superior Temporal Sulcus	Right	41	-47	35	-3

Table 2. Clusters where activity was significantly higher in the Retrieve than the Suppress condition during the scene cue. Voxel wise threshold of $p < 0.01$, cluster threshold of $p < 0.05$.

Region	Hemisphere	Voxels	Peak Voxel (MNI)		
			x	y	z
Middle Cingulate Cortex	Midline	131	-1	37	33
Thalamus	Midline	81	-3	5	-5
Precuneus	Midline	42	-13	65	27

Table 3. Clusters where activity was significantly higher in the Substitute than the Retrieve condition during the scene cue. Voxel wise threshold of $p < 0.01$, cluster threshold of $p < 0.05$.

Region	Hemisphere	Voxels	Peak Voxel (MNI)		
			x	y	z
PreCG	Left	179	37	-3	65
MCC	Midline	138	1	-21	39
IFG (BA 46)	Left	79	43	-27	37
AnG	Right	62	-63	59	23
MFG (BA 8)	Right	61	-43	-21	51
Precuneus	Midline	49	-1	61	43

Table 4. Clusters where activity was significantly higher in the Retrieve than the Substitute condition during the scene cue. Voxel wise threshold of $p < 0.01$, cluster threshold of $p < 0.05$.

Region	Hemisphere	Voxels	Peak Voxel (MNI)		
			x	y	z
Thalamus	Midline	73	-1	9	-9
Precuneus	Midline	62	-1	37	45

In addition to these regions, during the delay period greater activity was observed in the bilateral angular gyrus and the superior frontal gyrus (SFG) for the Suppress and Substitute conditions than the Retrieve condition (see Figure 8A). Interestingly, while there was some degree of overlap in the regions involved in Suppression and Substitution (e.g., SFG, left angular gyrus), I found robust hemispheric differences in the PFC for the two regulation conditions. Activity was lateralized such that the Substitute condition was associated with greater activity in the left PFC, whereas Suppression more strongly activated the right PFC (see Figure 8B for a conjunction map; see Tables 6, 7, 8 and 9 for a list of significant clusters). These findings are consistent with the hemispheric differences observed in Benoit and Anderson (2012).

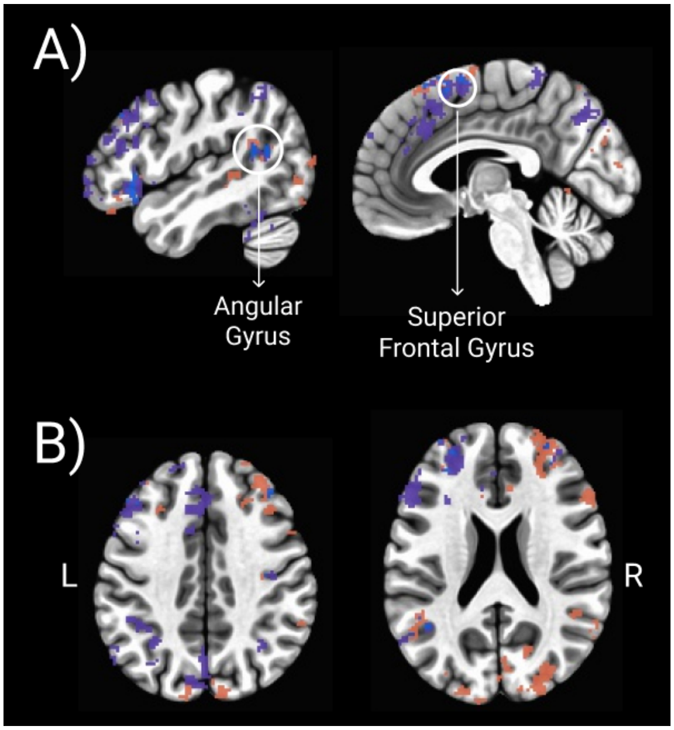


Figure 8. Univariate whole-brain data. Clusters where activity was higher in the Suppress (orange) and Substitute (purple) conditions relative to Retrieve condition. **A)** Suppression and Substitution activated overlapping regions in the left Angular Gyrus and SFG (blue). **B)** Retrieval suppression more strongly activated the right PFC (orange) whereas thought substitution was associated with left PFC activity (purple). Voxel-wise threshold $p < 0.01$, cluster threshold $p < 0.05$, 40 voxel cluster extent, overlaid on an MNI brain.

Table 5. Clusters where activity was significantly higher in the Suppress than the Retrieve condition in the middle of the delay period. Voxel wise threshold of $p < 0.01$, cluster threshold of $p < 0.05$.

Region	Hemisphere	Voxels	Peak Voxel (MNI)		
			x	y	z
Middle Frontal Gyrus (BA 9)	Right	855	-29	-61	23
Superior Temporal Sulcus	Right	622	-45	33	1
Superior Temporal Sulcus	Left	143	63	41	1
Supplementary Motor Area	Midline	477	-21	-11	71
Inferior Frontal Gyrus (BA 47/45)	Right	462	-55	-37	-11
Inferior Frontal Gyrus (BA 47/45)	Left	310	55	-33	-11
Inferior Frontal Gyrus (BA 44)	Right	102	-57	-27	23
Middle Temporal	Right	458	-63	59	17
Gyrus	Right	40	-41	55	3
Middle Temporal Gyrus	Left	130	51	59	21

Middle Occipital Gyrus	Right	433	-27	93	23
Fusiform Gyrus	Right	408	-23	87	-19
Fusiform Gyrus	Left	187	29	75	-19
Precuneus	Midline	176	-1	85	35
Precuneus	Midline	74	-7	63	61
Medial Superior Frontal Gyrus	Midline	135	-1	-27	61
	Left	130	1	61	-1
Cerebellum	Left	66	37	65	-21
	Left	42	11	41	-5
Superior Frontal Gyrus (BA 9/46)	Left	92	31	-57	25
Postcentral Gyrus	Right	82	-43	19	57
V5/MT	Right	66	-53	65	-1
Precentral Gyrus	Right	65	-43	-7	55
Middle Frontal Gyrus (BA 9)	Left	61	31	-51	35
	Left	45	39	-25	35
Superior Temporal Gyrus	Left	50	59	1	-15
Occipital Cortex	Left	47	25	95	23
Occipital Cortex	Right	46	15	99	27
Postcentral Gyrus	Left	41	17	29	61

Table 6. Clusters where activity was significantly higher in the Retrieve than the Suppress condition in the middle of the delay period. Voxel wise threshold of $p < 0.01$, cluster threshold of $p < 0.05$.

Region	Hemisphere	Voxels	Peak Voxel (MNI)		
			x	y	z
Middle Cingulate Cortex	Midline	64	-1	23	27
Putamen	Right	53	-27	-11	-7
Posterior Cingulate Cortex	Midline	52	-3	35	27

Table 7. Clusters where activity was significantly higher in the Substitute than the Retrieve condition in the middle of the delay period. Voxel wise threshold of $p < 0.01$, cluster threshold of $p < 0.05$.

Region	Hemisphere	Voxels	Peak Voxel (MNI)		
			x	y	z
Middle Frontal Gyrus (BA 6)	Left	1895	39	-3	65
Inferior Frontal Gyrus (BA 47)	Left	879	37	-63	5
	Left	412	51	-23	-9
Inferior Frontal Gyrus (BA 45)	Right	165	-51	-29	-11
Superior Parietal Lobule	Left	446	39	67	57

Fusiform Gyrus	Right	407	-43	71	-21
Fusiform Gyrus	Left	121	53	53	-27
	Left	53	59	63	-19
Middle Frontal Gyrus (BA 46)	Right	216	-43	-39	37
Inferior Parietal Lobule	Left	145	43	53	19
	Left	40	37	47	39
Inferior Parietal Lobule	Right	55	-39	67	55
Precuneus	Midline	138	1	69	43
	Midline	48	-1	83	39
Precentral Gyrus	Right	77	-35	-1	63
Middle Cingulate Cortex	Midline	72	7	-13	39
Cerebellum	Left	67	35	47	-33
Superior Frontal Gyrus	Right	67	-39	-23	55
	Right	62	-31	-63	7
Superior Frontal Gyrus	Left	48	15	-51	45
Inferior Temporal Gyrus	Left	55	57	39	-21
Orbitofrontal Cortex	Left	53	25	-47	-17

Middle Temporal Gyrus	Left	52	71	29	3
Temporoparietal Junction	Left	48	61	41	1

Table 8. Clusters where activity was significantly higher in the Retrieve than the Substitute condition in the middle of the delay period. Voxel wise threshold of $p < 0.01$, cluster threshold of $p < 0.05$.

Region	Hemisphere	Voxels	Peak Voxel (MNI)		
			x	y	z
Anterior Cingulate Cortex	Midline	49	1	-35	5
Supramarginal Gyrus	Right	40	-61	29	29

Question 2: Neural Correlates of Successful Memory Regulation

The second goal of the current study was to examine the neural correlates of *successful* memory regulation using eye-movement behavior as an online measure of the success of regulation. For this purpose, I examined whether activity in regions that were involved in memory regulation was modulated by viewing behavior. I correlated, across participants, activity in the Suppress and Substitute conditions in the ROIs described above with the mean proportion of viewing directed to the associate in the search display.

For the suppress condition, activity in the right dlPFC, vlPFC and IPL ROIs derived from Apšvalka et al. (2020) was moderately negatively correlated with the proportion of associate viewing, right dlPFC: $r = -0.26$, $p = 0.19$; right vlPFC: $r = -0.29$, $p = 0.16$; right SMA: $r = -0.08$, $p = 0.71$. A similar trend was observed in both ROIs derived from Benoit & Anderson (2012), right dlPFC: $r = -0.07$, $p = 0.72$; left vlPFC: $r = -0.32$, $p = 0.11$. Conversely, there was a positive correlation between activity in the left and right hippocampal ROIs and associate viewing, right hippocampus: $r = 0.26$, $p = 0.21$; left hippocampus: $r = 0.13$, $p = 0.52$.

In the Substitute condition there was a weak but positive correlation between activity in the right vlPFC and IPL ROI from Apšvalka et al. (2020), and associate viewing, right vlPFC: $r = 0.13$, $p = 0.50$; $r = 0.03$; $p = 0.88$, whereas in the right SMA and dlPFC, the correlation was negative, right SMA: $r = -0.10$, $p = 0.61$; right dlPFC: $r = -0.02$ $p = 0.91$. Similarly, there was a negative correlation between activity in PFC ROIs derived from Benoit & Anderson (2012) and viewing, right dlPFC: $r = -0.16$, $p = 0.43$; left vlPFC: $r = -0.13$, $p = 0.51$. Finally, there was a positive correlation between activity in the right hippocampus and viewing behavior, $r = 0.19$, $p = 0.34$, and a negative correlation between left hippocampus activity and viewing behavior, $r = -0.03$, $p = 0.90$ (see Figure 9). However, these correlations were not statistically significant for either condition.

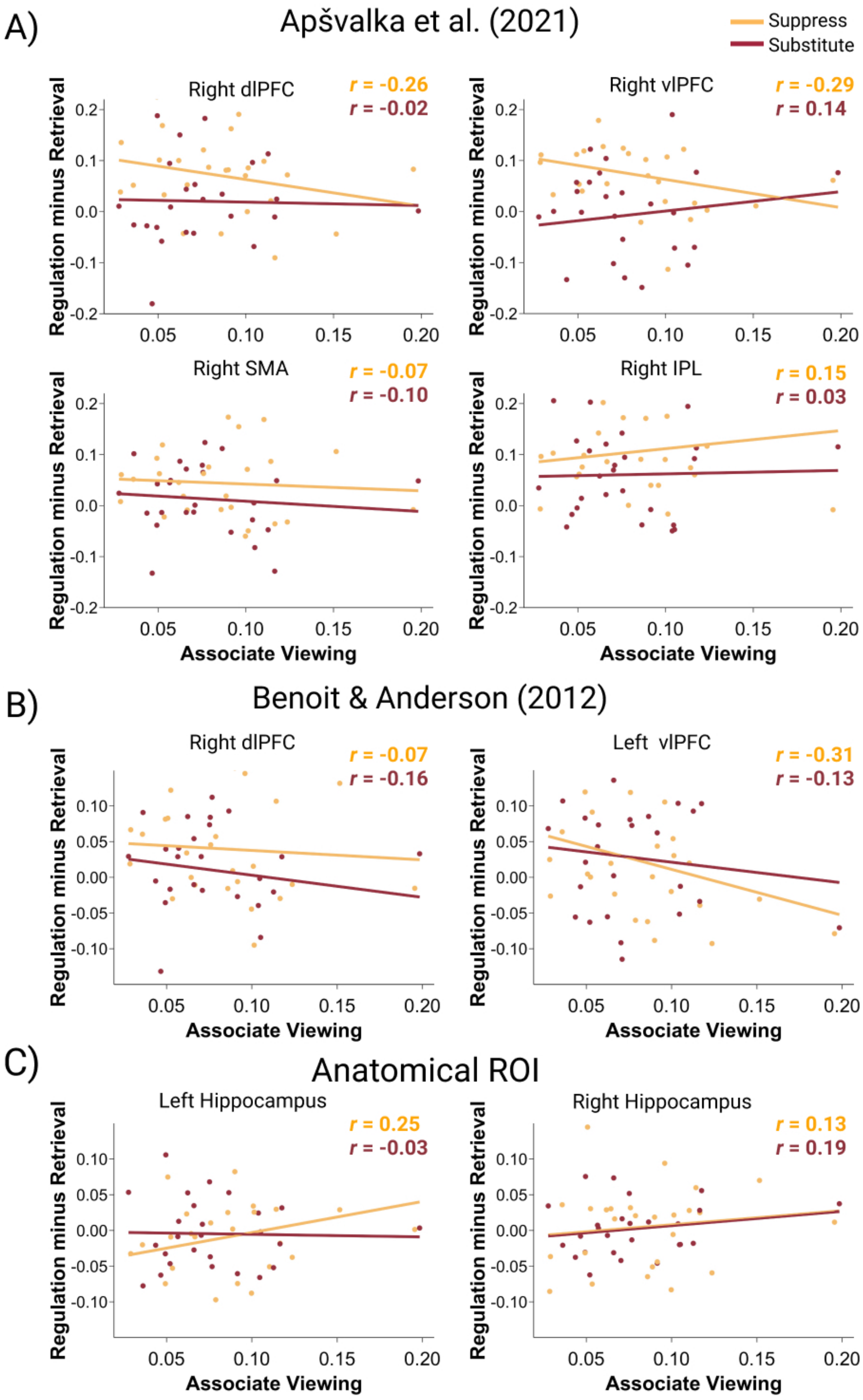


Figure 9. Viewing-related modulation in a priori ROIs. Correlations between activity in a priori ROIs with proportion of viewing directed to the associate.

I also examined regions outside these ROIs that may be sensitive to the success of memory regulation using a separate GLM. It may be expected that if prioritization of the associate in viewing behavior on a given trial is indicative of poor memory regulation in the Suppress and Substitute conditions, then this failure to exert successful control will be reflected in brain activity in regions that are involved in regulation. For this analysis, trials during the search phase were labelled based on whether the associate, or a non-associate object was prioritized (see section Object Prioritization above) and were analyzed separately in the GLM. This model consisted of 18 regressors of interest – the scene cue, delay, and search display onsets with trials sorted as a function of condition (Retrieve, Suppress, Substitute) and viewing (associate prioritized, non-associate prioritized). An additional regressor modelled all events from trials that were discarded due to bad viewing (i.e., less that 65% eye-tracking data available). Regressors modelling linear drifts and six demeaned head-motion parameters and their derivatives were included as regressors of no interest. Whole-brain analyses were conducted by contrasting trials in which the associate was prioritized, with trials in which a non-associate object was prioritized, separately for the Retrieve, Suppress and Substitute conditions. Contrast maps were thresholded at a voxel-wise threshold of $p < 0.01$.

In the Retrieve condition, activity in the primary visual cortex, precuneus and right vlPFC was higher when the associate was prioritized, compared to when a non-associate object was prioritized. In the Suppress condition, a similar pattern was observed in the IPL, superior temporal sulcus (STS) and inferior temporal gyrus in the right hemisphere. Finally, in the Substitute condition, the opposite pattern (i.e., greater activity in trials where a non-associate object was prioritized) was evident in the right orbitofrontal cortex, SFG and the middle cingulate cortex. However, these clusters were not significant following cluster correction.

Question 3: Effect of Memory Regulation on Neural Reinstatement in the MTL

The final goal of the study was to examine the effect of memory regulation on MTL reinstatement of encoded information using RSA. Reinstatement was measured as the correlation between trial-specific activity from the search phase, with “representational templates” of each object derived from the pre-exposure phase.

Derivation of Representational Templates

To ensure that beta values were extracted from precise anatomical structures, all RSA analyses were conducted in participants’ native (i.e., non-normalized) space. Pre-exposure data was preprocessed using the same steps described above (removal of first four TRs, slice-time correction, motion-correction, alignment to anatomical scan, and smoothing using a 4mm FWHM Gaussian kernel). Scans from the pre-exposure phase were aligned to the T1 image collected during the search phase. This was done to ensure that search phase and pre-exposure phase EPIs were in the same space. Alignment between the pre-exposure EPIs and the search phase T1s, and between pre-exposure and search phase EPIs was verified using visual inspection. Concatenated preprocessed runs were analyzed using 3dDeconvolve. The regression model consisted of 11 regressors – one regressor each for the three faces, three tools, and three scenes presented during the pre-exposure phase, as well as one regressor modelling the presentation of the “targets” (i.e., immediate repeats for the 1-back task), and one regressor modelling button-press responses. Regressors modelling linear drifts and six demeaned head-motion parameters, and their derivatives were included as regressors of no interest. Beta-maps corresponding to each object served as the representational template for that object.

Trial-by-trial Search Phase Models

The least-squares single approach was used to extract trial-specific activity from the search phase (Mumford et al., 2012). In this method one GLM is conducted per trial. The GLM of each trial consists of one regressor modelling the event of interest of that trial, and additional regressors modelling all other events and trials. Following this approach, for each GLM, I included one regressor modelling the middle of the delay period of a given trial, three regressors modelling the delay period of the remaining trials separately for each condition, and three regressors each, modelling the scene cue and search display for all trials separately for each condition. To reduce computation time, search runs were not concatenated. Only one run containing the current trial was processed in each GLM (e.g., only Run 1 was included for computing activity for Trial 1 of Run 1, only Run 2 was included for Trial 1 of Run 2 and so on). This approach is consistent with past work that has used FSL and SPM for modelling trial-specific activity (e.g., Zhao et al., 2021; Mack & Preston, 2016; Libby et al., 2014).

Computing Pattern Similarity

Before extracting representational templates and trial-specific activity, the output from the pre-exposure and search phase GLMs was multiplied with whole-brain masks derived from the preprocessing of both phases. This was done to ensure that beta-values were only extracted from voxels that had valid data in both the pre-exposure and search phase. For each participant representational templates (beta values) corresponding to the three faces and three tools were extracted from the pre-exposure phase from the left and right hippocampus and perirhinal cortex (PrC) derived from the participant's Freesurfer segmentation. Next trial-specific activity from the middle of the delay period in the search phase was extracted from the same anatomical masks. Finally, reinstatement on each trial was quantified by calculating a Pearson's correlation between the trial-specific beta values from each voxel within a region of interest and the corresponding beta values from the representational template of each object. Correlation values were Fisher-z transformed. Only trials with correct responses in the hybrid encode-and-test procedure were carried forward for the RSA analyses.

Pattern Similarity with Associate. I first examined the effect of memory retrieval and regulation on the reinstatement of the associate object. For this purpose, pattern similarity for each ROI (left and right hippocampus and PrC) with the representational template of the associate was averaged across trials separately for the three conditions (Retrieve, Suppress and Substitute) and associate categories (Face and Tool). Pairwise post-hoc t-tests were used to compare pattern similarity between conditions separately for Faces and Tools to test whether memory regulation reduced the reinstatement of the associate.

Interestingly, in the bilateral Hippocampus and the left PrC, the pattern of associate reactivation between conditions for faces was opposite to that observed for tools. In these regions, associate reactivation in trials where the associate was a face was numerically higher in the Retrieve compared to the Suppress and Substitute conditions. This pattern was significant for the difference between the Retrieve and Substitute condition in the right Hippocampus, $t(25) = 2.31$, uncorrected $p = 0.02$, $d = 0.48$. All other pairwise differences were not statistically significant, t's ≤ 1.56, p's ≥ 0.13, d's ≤ 0.43. Contrarily, for trials where the associate was a tool, reinstatement was consistently lower in the Retrieve relative to the Suppress and Substitute conditions (see Figure 10). In the right Hippocampus, associate reactivation was significantly lower in the Retrieve and Suppress relative to the Substitute condition, t's ≥ 2.81, p's < 0.02, d's ≥ 0.75. All other pairwise comparisons were not significant t's $\leq 1.1.58$, p's ≥ 0.13, d's ≤ 0.39. In the right PrC, associate reactivation was numerically highest in the Suppress condition for both faces and tools. However, once again, these pairwise differences were not significant *t*'s ≤ 1.53, *p*'s ≥ 0.14, *d*'s ≤ 0.43.

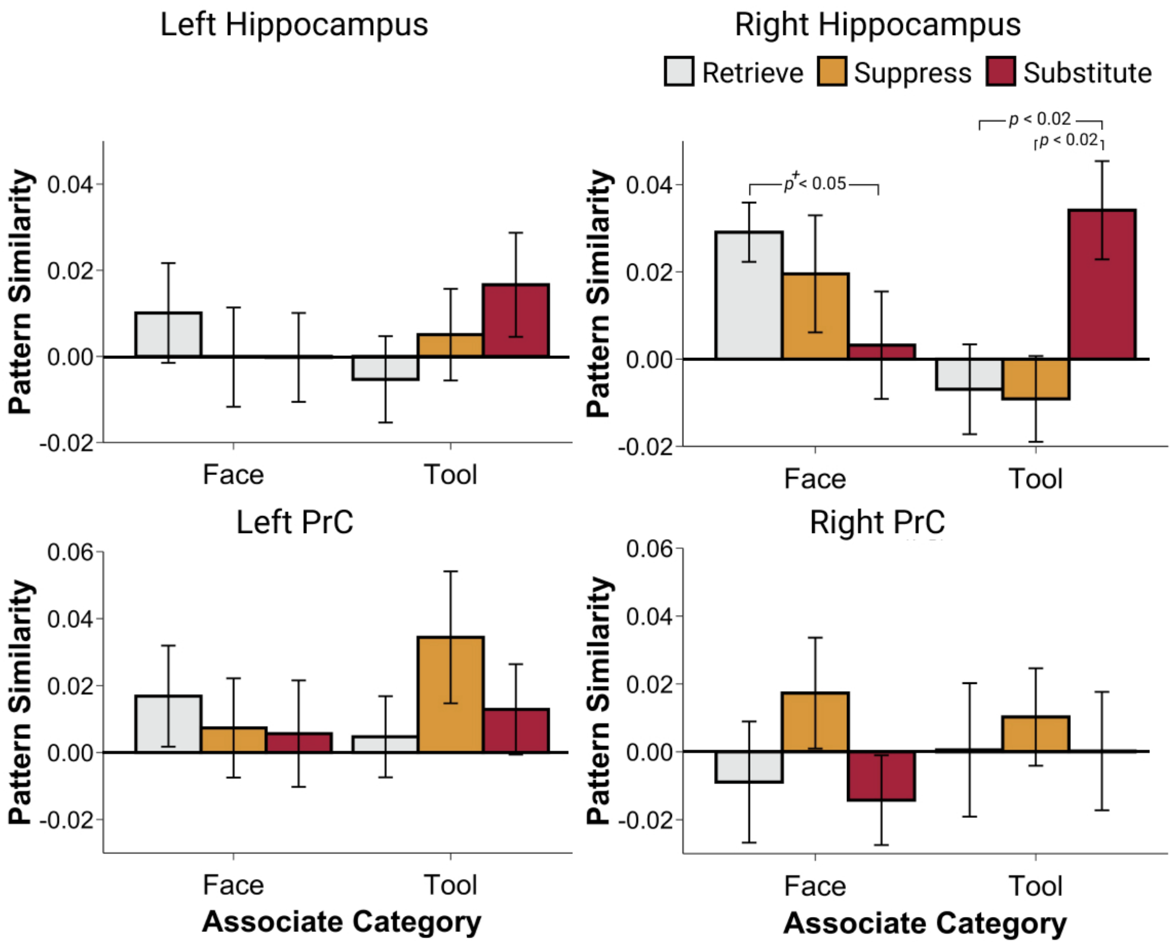


Figure 10. Associate reactivation in the medial temporal lobe. Pattern similarity with representational template of the associate in the left and right Hippocampus (top) and the PrC (Bottom). $^+$ uncorrected *p*.

Pattern Similarity with Prioritized Associate. In the current study, eye-movements dedicated to the associate embedded in the search display were used as an index of the success of memory retrieval and regulation. If eye-movement behavior reflects the object that was retrieved and held active during the delay period (i.e., prior to the presentation of the search display), it may be expected that pattern similarity with the associate would be higher in trials where the associate was the prioritized object, as compared to trials where a non-associate object was prioritized. To test this possibility, I labelled trials based on whether the associate was prioritized, and compared pattern similarity between associate prioritized and non-associate prioritized trials, separately for the three conditions and associate categories. Pairwise differences in pattern similarity between associate prioritized and non-prioritized trials were not significant, t's ≤ 1.73, p's ≥ 0.09, d's ≥ 0.44. However, in the left PrC, pattern similarity with the associate was numerically higher for trials in which the associate was prioritized, compared to trials in which a non-associate object was prioritized (see Figure 12).

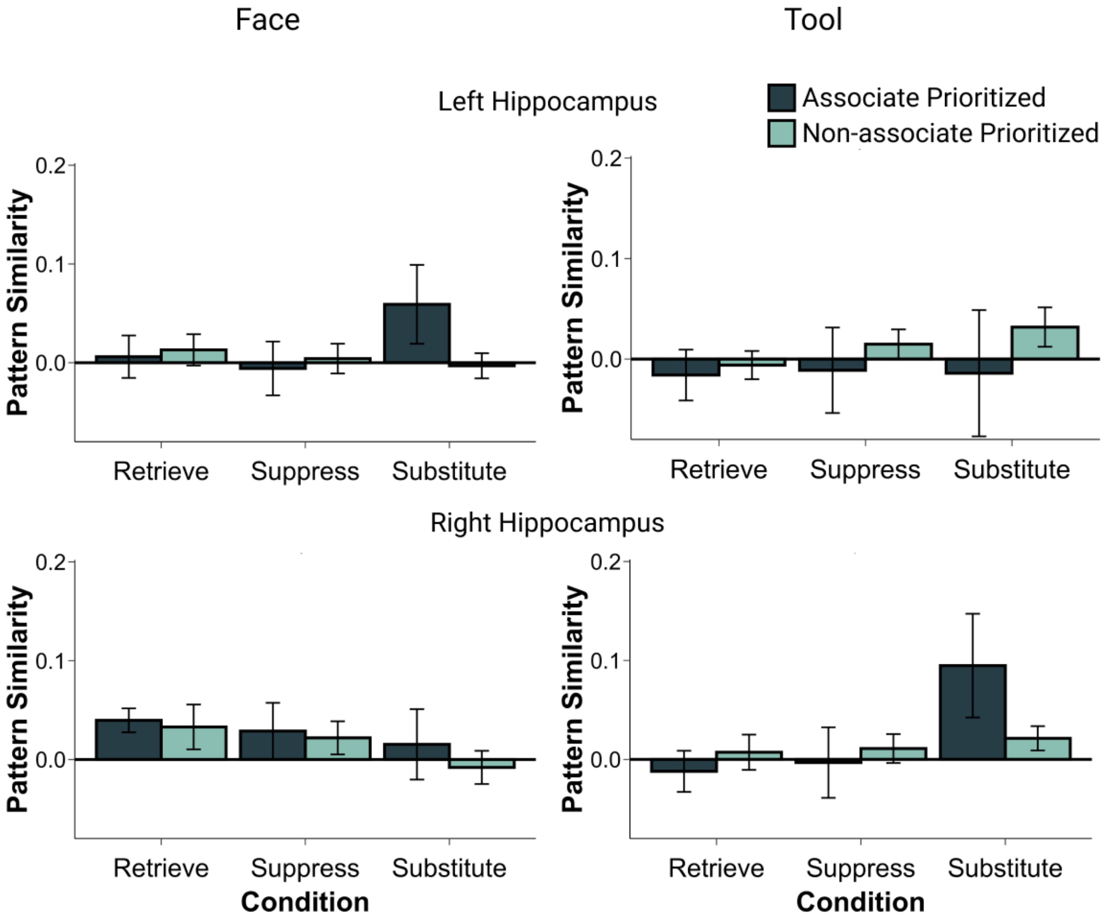


Figure 11. Viewing-related modulation of associate reactivation in the hippocampus. Pattern similarity with the representational template of the associate, conditionalized on viewing-based prioritization in the left and right Hippocampus separately for faces (left) and tools (right).

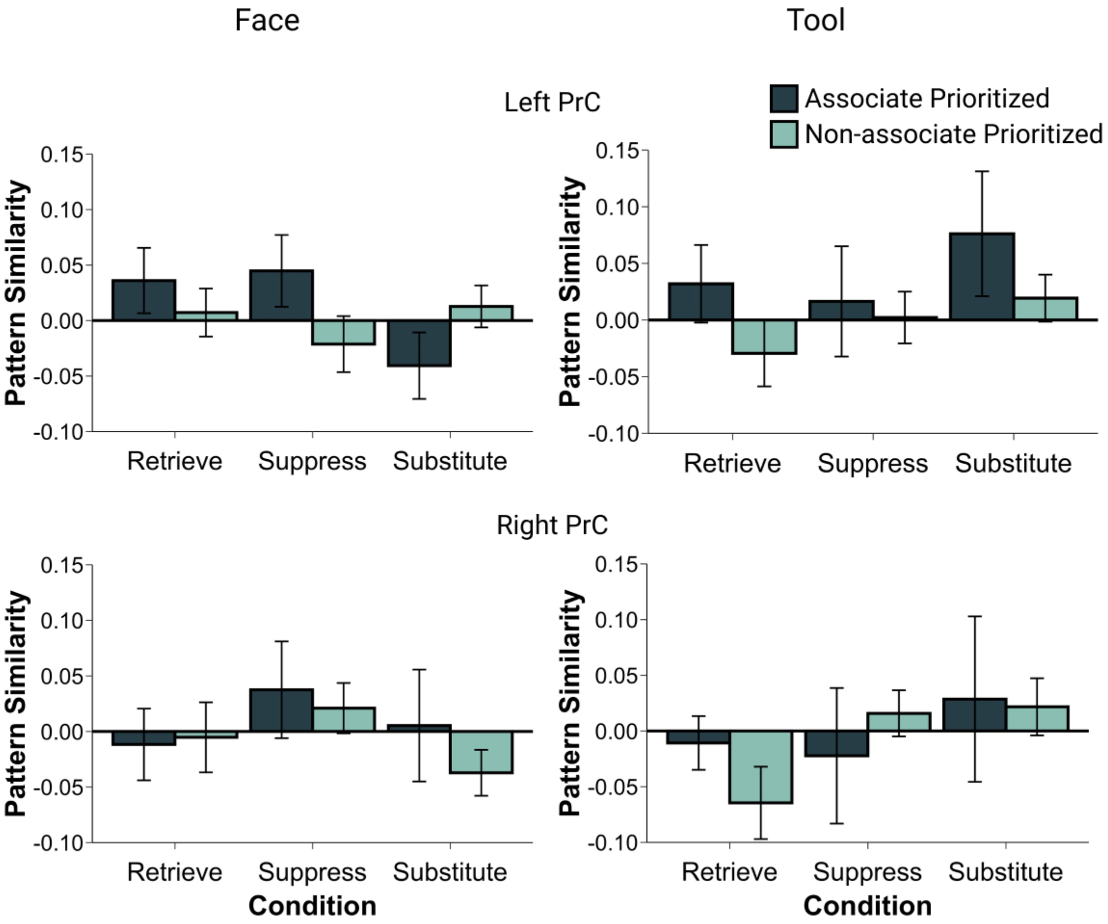


Figure 12. Viewing-related modulation of associate reactivation in the perirhinal cortex. Pattern similarity with the representational template of the associate, conditionalized on viewing-based prioritization in the left and right PrC separately for faces (left) and tools (right).

Pattern Similarity in the Substitute Condition. The final goal of this study was to investigate whether thought substitution is associated with an upregulation of the representation in the MTL of the object chosen by participants as a substitute on a trial-by-trial basis. To test this, for all trials in the substitute condition, I identified the object that was prioritized (i.e., most viewed) in the search display. Next, in the subset of trials in which an opposite-category object was prioritized, two pattern similarity indices were calculated- similarity with the representational template of *associate* object, and pattern similarity with the representational template of the *prioritized opposite category* object. These similarity values were then compared using a paired t-test separately for faces and tools. In the left and right Hippocampus and PrC for faces, and the right hippocampus and bilateral PrC for tools, pattern similarity with the template of the prioritized opposite category object was numerically higher than with the template of the associate (see Figure 13). In the left hippocampus, the opposite pattern was evident for tools, in that pattern similarity was greater with the associate, relative to the prioritized opposite category object. These pairwise differences were, however, not significant t's ≤ 1.74, p's ≥ 0.09, d's ≤ 0.35.

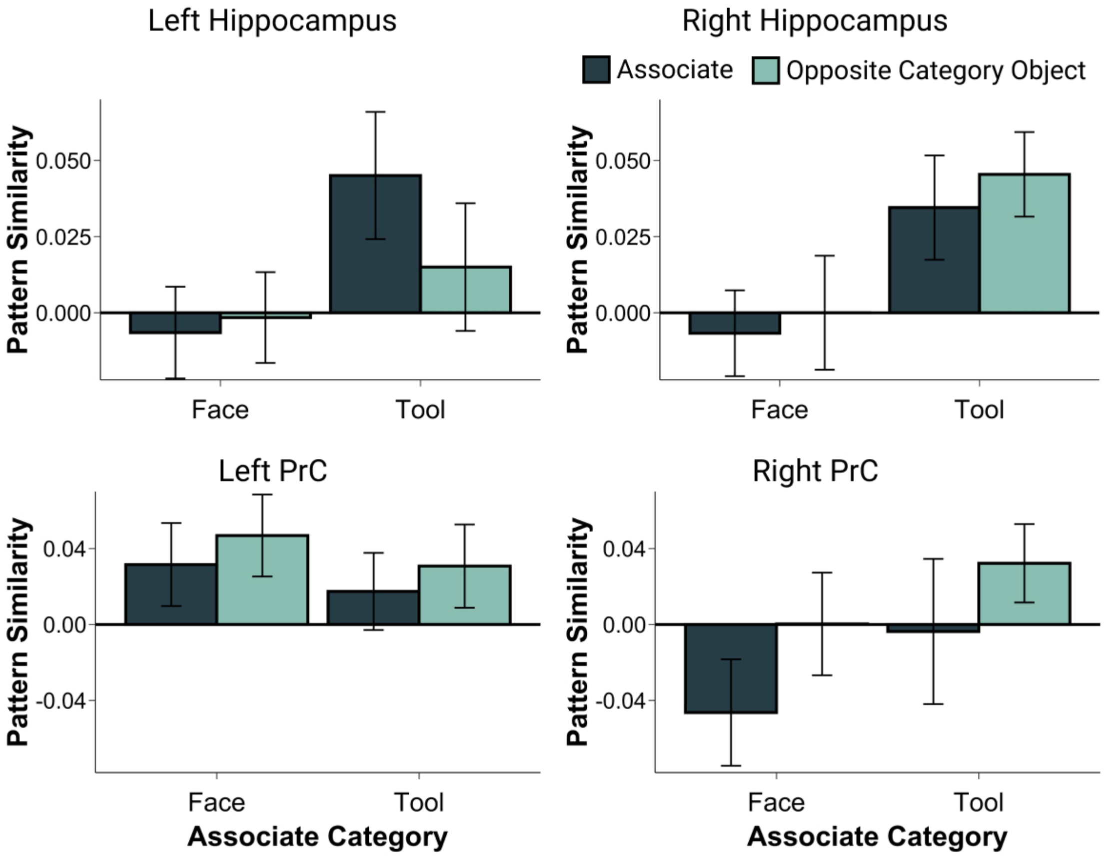


Figure 13. Reinstatement in the Substitute condition. Pattern similarity with the representational template of the associate (dark green) and the prioritized object from the opposite category as the associate (light green) for trials in the Substitute condition in the Hippocampus (top) and the PrC (bottom).

The results from the final aim, suggest that reinstatement of encoded information in the MTL is affected by attempts to regulate memory retrieval. This is evidenced by lower pattern similarity with the associate template in the bilateral hippocampus in trials where the associate was a face in the Suppress and Substitute conditions. Strikingly, the opposite pattern was observed for trials where the associate was a tool.

Discussion

The current study aimed to examine three open questions in the field of episodic memory regulation. First, what are the neural correlates of *self-directed* thought substitution? Second, what are the processes involved in *successful* memory regulation? Finally, what is the effect of the two strategies of memory regulation on neural reinstatement of encoded information in the MTL? I capitalized on previously established links between eye-movements and memory, and used viewing behavior as an incidental, online index of memory retrieval and regulation in a novel paradigm designed to probe direct suppression and thought substitution. Participants first encoded three faces and three tools with several scenes. After encoding, they completed a memory regulation and search phase during which they were presented with scene cues along with an instruction to either retrieve, suppress or substitute the memory of the associate of the scene while undergoing concurrent eye-tracking and fMRI. This was followed by the presentation of a search display consisting of the encoded objects which were irrelevant to the instructed search task. However, incidental viewing directed to the objects in the search display was used as an index of memory retrieval and memory regulation success. Finally, participants completed a recognition memory test during which they were presented with encoded scenes, and were instructed to select the associate from amongst the six possible alternatives (three faces and three tools). Performance in this part of the experiment was used to examine whether there was any memory enhancement associated with retrieval of the matching object, or any memory decrement associated with regulation during the search phase.

Behavioral results revealed that memory regulation led to a decrement in memory performance in the final recognition memory phase. However, this effect was limited to pairs where the associate was a tool. There was no difference in accuracy between conditions for pairs in which the associate was a face. Eye-tracking data indicated that for both faces and tools, viewing directed to the associate was downregulated in the suppress and substitute conditions, relative to the retrieve condition. On the other hand, viewing-based prioritization of an object from the opposite category was highest in the substitute condition, where participants were explicitly instructed to call to mind a specific object from the opposite category as the associate.

To examine brain regions involved in memory regulation, I first probed ROIs that were previously identified to be involved in memory regulation in studies using the TNT task (Apšvalka et al. 2020; Benoit & Anderson, 2012). These results replicated the finding that activity in the right prefrontal cortex was significantly higher in the suppress, but not the substitute condition, relative to the retrieve condition, whereas activity in the left PFC was higher in the substitute condition. Contrary to past work (Anderson et al., 2004), however, I did not find a reduction in hippocampal activity in the suppress condition. Further, activity differences in these regions were moderately correlated with the success of memory regulation, as measured by viewing behavior, but these correlations were not significant. Whole-brain analyses also revealed extensive activity outside these a priori ROIs that was lateralized to the right hemisphere in the suppress condition, and to the left hemisphere in the substitute condition. Finally, RSA was used to examine the effect of memory regulation on the neural reinstatement of encoded information in the MTL. Results from this analysis indicated an opposite pattern for faces and tools.

Associate reactivation in the right hippocampus was higher in the retrieve condition compared to the suppress and substitute conditions for trials where the associate was a face. However, reactivation of tool associates was significantly higher in the suppress and substitute conditions, relative to the retrieve condition.

Eye-movements Are Sensitive to Memory Regulation and May Index Active Representations

Past work has shown that the eye-movement-based memory effect is evident across a range of task demands. Disproportionate viewing of items retrieved from memory is evident when memory cues are presented subliminally (Nickel et al., 2015), when participants are instructed to conceal their memories (Mahoney et al., 2018), when they are instructed to ignore the retrieved items in search displays (Nickel et al., 2020), and when explicit recognition fails (Hannula et al., 2012; Hannula & Ranganath, 2009). However, whether this effect persists when participants are instructed to exert top-down control on memory processing is still unclear. One recent study used eye-tracking while participants completed a directed forgetting task and found that patterns of eye-movements distinguished information that had been forgotten as a result of top-down control, from information that had been incidentally forgotten (Whitlock et al., 2020). In a typical directed forgetting task, participants first complete a study phase during which they are exposed to some information (e.g., words, pictures). A subset of trials in the study phase are accompanied by a forget cue, and participants are instructed to attempt to forget the information, and are told that memory for this information will not be tested. During the test phase, however, all stimuli are tested regardless of the remember/forget instruction in the study phase. Memory on the final recognition phase is typically worse for items that were accompanied by an instruction to forget (forget-items), compared to items that participants were instructed to remember (remember-items; Bancroft et al., 2013; Hockley et al., 2016; for a review see Sahakyan & Foster, 2016). It has been suggested that directed forgetting is effortful and requires top-down inhibitory control during encoding (Anderson & Hanslmayr, 2014; Fawcett & Taylor, 2010; Wylie et al., 2008). Using this paradigm, Whitlock et al. (2020) found that eye-movements directed to the forget-items are significantly reduced relative to remember-items, only when the item is successfully forgotten. Moreover, viewing to purposely forgotten items (i.e., items that were accompanied by a forget cue during encoding) is even lower than items in the remember condition that were incidentally forgotten, suggesting that exerting top-down inhibitory control during encoding impairs the memory beyond what is observed in incidental forgetting, and that eye-movements can distinguish between these forms of forgetting.

The current study extends these findings by demonstrating that top-down control of retrieval also downregulates viewing directed to retrieved information. Unlike in Whitlock et al. (2020) who examined how exerting control during encoding affects eye-movements during subsequent retrieval, here, this effect was present while participants were attempting to control memory retrieval itself. This was evidenced by the fact that viewing to the associate of the scene cue was significantly reduced in the suppress and substitute conditions relative to the retrieve condition. Furthermore, I found that viewing of an opposite category object was higher in the substitute condition, when participants were instructed to call to mind a specific object from the opposite category. This effect was evident regardless of the category that participants were using for substitution. This suggests that memory-based eye-movements are sensitive to top-down control, and may index representations that are actively held in mind by participants on a trial-by-trial basis. Further evidence for this comes from the RSA analysis of the substitute trials. Here, the non-associate object that was prioritized in viewing behavior was identified for each trial. I found that compared to the associate, pattern similarity was numerically higher with the representational template of this prioritized non-associate object (Figure 13). It is possible that representations activated in the medial temporal lobe may drive oculomotor behavior causing eye-movements to be drawn to the information that is being actively represented. Future studies might examine the neural mechanisms underlying this interaction between the MTL and the brain regions that control eye-movement behavior (Hannula, 2018) in the context of memory retrieval and regulation.

Suppression and Substitution Activate Distinct Brain Regions

The design in the current study permitted me to directly compare the neural correlates of retrieval suppression and thought substitution. Univariate analyses from these conditions revealed that the two strategies were associated with activity differences in distinct, hemispherically lateralized regions in the frontal cortex. Retrieval suppression was associated with higher activity in the right dorsolateral and ventrolateral PFC, as well as the inferior frontal gyrus, whereas thought substitution more strongly activated the left ventrolateral PFC. This hemispheric dissociation is consistent with results from a past study that also compared retrieval suppression and thought substitution (Benoit & Anderson, 2012). In contrast to Benoit and Anderson (2012), however, in the current study I also found extensive, lateralized activation that was associated with one of the two conditions outside the ROIs that were previously probed. This could be due to two reasons – first, unlike Benoit and Anderson (2012), the current study used a within-subjects design, potentially providing more power to detect between-strategy differences. Second, brain activity differences reported in Benoit and Anderson (2012) came from the presentation of the memory cue. As described above, in the encoding phase of the TNT task, participant learn several cue-target word pairs. Then, in the TNT phase, they are presented with cue words in either green or red, which indicates to the participant that they should either recall the target (green; think condition) or push the target out of awareness (red; no-think condition). This design only permits the modelling of the memory cue presentation in each trial of the TNT phase. Episodic memory regulation involves the inhibition of retrieval, which is a prepotent response (Anderson et al., 2016; Anderson & Huddleston, 2012; Anderson, 2003). This process recruits neural mechanisms similar to those required for response inhibition. Evidence from the response inhibition literature suggests that this process requires some time to be upregulated (Lingnau & Vorberg, 2005; Kiefer et al., 1998). If it is the case that cognitive control mechanisms take some time to be fully engaged, then it may be expected that activity in the regions responsible for this process may peak a little while after the presentation of the cue. Indeed, one study reported that suppression was more effective when the think/no-think instruction was given in advance of the memory cue, suggesting that participants benefit from additional preparatory time to implement the no-think instruction (Hanslmayr et al., 2010).

The design in the current study permitted me to separately model two time points in the trial (the presentation of the scene cue, and the middle of the delay period). Results from the scene-cue, which is the trial period that is most often modeled in past studies using the TNT task, exhibited a similar pattern to that reported by Benoit & Anderson (2012), i.e., higher activity in the right dlPFC for suppress trials, and higher activity in the left vlPFC in the substitute condition. However, exploratory whole-brain analyses revealed more extensive activation in the delay period (Tables 5 and 7) compared to the presentation of the scene cue (Tables 1 and 3). This may suggest that some regions involved in memory regulation come online after the presentation of the suppression instruction and memory cue.

The distinct networks involved in these strategies may underlie the contrasting task demands of retrieval suppression and thought substitution. The right hemisphere dominance for retrieval suppression has been previously reported (e.g., Benoit et al., 2015; Gagnepain et al., 2014; Anderson et al., 2004). It has been suggested that retrieval suppression represents a special case of a domain-general inhibition mechanism that is flexibly recruited for top-down control across different domains including response inhibition (Rae et al., 2014; Zhang et al., 2017), and emotion regulation (Depue et al., 2007; for a review see Anderson & Huddleston, 2012). A recent study by Apšvalka et al. (2020) lends support to this hypothesis through three key sets of results. First, Apšvalka et al. (2020) found that the TNT and go/no-go tasks (probing retrieval suppression and response inhibition, respectively) activated overlapping regions in the right PFC. Second, a pattern classification analysis revealed that a model trained on activity in the PFC from the go/no-go task reliably discriminated think from no-think trials in the TNT task. Third, connectivity analyses using the same seed region in the PFC indicated higher connectivity with the motor cortex relative to the hippocampus during the go/no-go task, whereas during the TNT task, connectivity was higher with the hippocampus. Taken together, these results suggest that regions in the right PFC may represent hubs involved in a domain-general inhibitory mechanism that flexibly alter connectivity with target regions based on task-demands.

Although thought substitution had similar behavioral consequences to retrieval suppression (i.e., decrement in recognition memory and reduced viewing directed to the associate), the process elicited activity in distinct brain regions, including the dorsolateral and ventrolateral PFC, and the inferior and superior parietal lobes in the left hemisphere. In the past, thought substitution has been investigated using a modified version of the TNT task (Hertel & Calcaterra, 2005; Benoit & Anderson, 2012). Here, participants learn two targets associated with each cue. Then in the TNT phase, they are instructed to substitute the memory of the first paired associate of the cue with the second one. In Benoit and Anderson (2012), this task was associated with increased activity in two regions in the left hemisphere – the vlPFC and caudal PFC. In the current study, the experiment was designed to permit participants to self-generate a thought substitute on a trial-by-trial basis, rather than select the substitute from one of two associates paired with the same item. This was done to more closely resemble the process of thought substitution in the real world, where we often choose the information we use for substitution (Hotta & Kawaguchi, 2009). For this, participants were instructed to substitute the memory of the associate of the scene with a specific object of their choosing from the opposite category as the associate. Although this design provided participants with some flexibility in terms of the information they chose for substitution, it introduced one major difference from the modified TNT task. Here, in order for participants to know which category they should use for substitution, they were necessarily required to first retrieve the associate of the scene cue. It is possible that some of the activity in this condition observed in the current study was associated with the requirement in our task to specifically resolve competition after having first retrieved the associate. Consistent with this idea, it has been suggested that activity in the IPL mediates attention capture by retrieved memory (Vincent et al., 2006), whereas activity in the SPL underlies top-down orienting of attention to internal memory representations (Polyn et al., 2005; see Ciaramelli & Moscovitch, 2020 and Ciaramelli et al., 2008 for reviews). Both these regions exhibited significantly higher activity in the substitute, but not the suppress condition, relative to the retrieve condition in the current study. Similarly, activity in the left vlPFC has been consistently reported in studies using the retrieval-induced forgetting paradigm – a task that requires participants to select one of several competing memory representations (Wimber et al., 2008; Kuhl et al., 2008). In this task, participants first encode several exemplars from a certain semantic category (e.g., SPORT-tennis, SPORT-hockey, FRUIT-orange, FRUIT-kiwi). Then, in a retrieval practice phase, they are presented with category information and are instructed to rehearse only a subset of the exemplars based on cues (e.g., FRUIT-ki____). Results from this task show that memory for practiced exemplars (FRUIT-kiwi) is better than memory for items from categories that were not used in the retrieval practice phase (SPORT), whereas memory for non-practiced exemplars (FRUIT-orange) is worse (Anderson et al., 2000; Wimber et al., 2008; Kuhl et al., 2008; Spitzer and Baüml, 2007; Spitzer 2014). It has been suggested that this effect is driven by top-down inhibition of memory of competing exemplars from the retrieved categories by regions including the anterior cingulate cortex and the left vlPFC (Kuhl et al., 2007; Wimber et al., 2008; 2015; see Murayama et al., 2014 for a meta-analysis), both regions that showed significantly higher activity selectively in the substitute condition in the current study. These results support the idea that activation of the left lateral PFC observed in the current study may underlie the requirement in thought substitution to resolve competition between the retrieved object, and the object chosen for substitution. Additionally, activity in the parietal lobe, which has not been previously reported in studies on thought substitution, may be involved in shifting attention from the representation of the retrieved associate to the substitute object that is self-generated by the participant.

To summarize, results from the current study demonstrated that retrieval suppression and thought substitution activated distinct brain regions in the right and left PFC, respectively. In addition, the thought substitution condition was also associated with increased activity in the parietal lobe. These findings indicate that the two strategies of memory regulation are subserved by independent neural mechanisms that may support their differing task demands.

Activity in Control Regions Was Not Sensitive to Regulation Success

One novel aspect of the current study was the use of an online, incidental measure of the success of memory regulation. In most past TNT studies, memory performance in the final recall phase is used as an index of how well participants were regulating their memories in the TNT phase. Although memory decrement for suppressed information is often observed in these studies, the size of the effect is quite variable (Anderson & Huddleston, 2012; see Bulevich et al., 2006; Bergström et al., 2007 for instances where no forgetting was observed). As such, final memory performance may be a coarse measure of regulation success. An online measure may be more sensitive to detecting idiosyncratic changes in regulation success on a trial-by-trial basis. One past study used explicit reports as an online index of regulation. In this study by Benoit et al. (2015), participants were instructed to report on each no-think trial how successful they were in suppressing the memory of the associate. Results revealed that participants reported intrusions of the associate on up to 30% of trials, particularly on the first presentation of the pair. Furthermore, activity in the dlPFC varied as a function of intrusion, such that activation was higher on trials where participants reported intrusions.

The current study demonstrates that eye-movement behavior may be another good online index not only of retrieval as is suggested by past work (e.g., Hannula et al., 2006) but also of memory regulation, since eye-movements were affected by what participants were instructed to do when scenes were presented. Overall, viewing directed to the associate was significantly reduced in the suppress and substitute conditions, as compared to the retrieve condition. However, the viewing-based prioritization analysis revealed that in approximately 20% of trials in the regulation conditions, participants directed disproportionate viewing to the associate, suggesting that at least in a few trials, participants were unable to successfully regulate retrieval of the associate object (Figure 5).

To examine whether, similar to Benoit et al. (2015), activity in control regions involved in memory regulation was sensitive to the success of regulation, I correlated across participants, activity in these regions with the proportion of viewing dedicated to the associate in the suppress and substitute conditions. If activity in control regions was modulated by regulation success, then it may be expected that brain activity would be higher amongst participants who dedicated lower viewing to the associate (possibly indexing successful regulation). However, in the current study, there was no correlation between brain activity and viewing behavior. The correlational analysis used here did not leverage trial-by-trial differences in regulation success within a participant. It is possible that averaging brain activity across trials may obscure subtle differences in brain activity that are evident at the level of individual trials. Thus, correlating brain activity and viewing behavior at the level of individual trials (*within* a participant) rather than averaging across trials may be more sensitive to detecting modulation of brain activity by regulation success. Future analyses might also examine whether different metrics (e.g., the connectivity between control regions and the hippocampus), rather than univariate activity, are more sensitive to regulation success as measured using eye-movement behavior.

Reactivation of Tool Associates May Lead to Improved Forgetting

One intriguing finding from the current study was that differences in associate reinstatement in the hippocampus between conditions depended on the category of the associate. For pairs in which the associate was a face, pattern similarity with the template of the associate was highest in the retrieve condition, as compared to the suppress and substitute conditions. Conversely, for tools pattern similarity with the associate was lowest in the retrieve condition

(Figure 10). Past work has demonstrated that memory regulation leads to a reduction in associate reinstatement, which is linked with worse memory (Wimber et al., 2015). Based on these results, it would be expected that memory for regulated face associates would be impaired, since reactivation of face associates was lower in the suppress and substitute conditions. On the other hand, memory for tool associates should be intact, given that tool reactivation was higher in the suppress and substitute conditions. However, here I found the opposite pattern such that memory for regulated pairs was worse for tools, but not for faces relative to the respective baseline trials. This suggests that *higher* reactivation of regulated tool associates led to *worse* memory performance. These contradictory findings may be reconciled under a recent computational model that proposes that there is a U-shaped (rather than linear) relationship between memory reactivation and memory strengthening. According to the non-monotonic plasticity hypothesis (Norman et al., 2006; 2007; Newman & Norman, 2010), high levels of memory reactivation lead to strengthening of the memory, whereas low levels of reactivation leave memory strength unchanged. Counterintuitively, moderate levels of reactivation put the memory in a state that is susceptible to be altered by factors such as top-down control, leading to weakening of the memory strength (for a review see Ritvo et al., 2019).

This proposal has been tested in a study by Detre et al. (2013) using the standard TNT task. In this study, participants encoded words with pictures of faces, scenes, cars and shoes. In the TNT phase, they were presented with word cues along with an instruction to either retrieve the associated picture (think condition), or to push it out of awareness (no-think condition). Similar to the current study, participants in Detre et al. (2013) completed a functional localizer scan during which they were presented with pictures of exemplars from the four categories used in the study phase. A ridge regression model was trained on the localizer scans to detect activity patterns associated with processing each of the four categories. This model was applied to each trial from the TNT task to measure the extent of reactivation on a given trial. This measure was then related to recall performance on a subsequent memory test. Using a novel Bayesian curve-fitting procedure, Detre et al. (2013) demonstrated that the relationship between associate reactivation and memory strength was, in fact, U-shaped. Final memory performance was lower for trials that showed moderate levels of memory reactivation during the TNT phase as compared to trials with very low and very high levels of reactivation. Recent studies have shown that this model predicts level of forgetting across a range of tasks, including retrieval-induced forgetting (Wang et al., 2019) and working memory suppression (Lewis-Peacock & Norman, 2014). Moreover, this relationship between reactivation and memory strength is suggested to underlie the variability observed in the memory decrement for no-think items observed across TNT studies (Anderson & Huddleston, 2012).

In the current study, two pieces of preliminary evidence might suggest moderate reactivation of tools as compared to faces. First, memory for pairs where the associate was a tool was significantly worse than faces in the hybrid encode-and-test procedure, i.e., prior to the memory regulation and search phase. A recent study demonstrated that forgetting of no-think items in the TNT task is better when baseline learning is low (Rogers, 2021). Additionally, past work suggests that memory reinstatement in the MTL correlates with accuracy (Tompary et al., 2016; Thakral et al., 2015). Hence it is possible that poorer encoding of pairs where the associate was a tool relative to faces could have led to lower levels of tool reinstatement. Second, there was a main effect of associate category on viewing directed to the associate object, such that regardless of condition (retrieve, suppress or substitute), viewing directed to tool associates was lower than faces. If it is the case that viewing behavior reflects strength of retrieved memory trace (Whitlock et al., 2020), then it may be expected that the strength of reactivation was lower for tools as compared to faces. These results may suggest that the level of reactivation of tools in the suppress and substitute conditions pushed these memories into the “dip” of the U-shaped curve, making them more likely to be modified by cognitive control mechanisms and subsequently forgotten. This hypothesis, of course, would need to be directly tested in the future using the current dataset.

Limitations and Future Directions

One effect that was not reliably replicated in the current study was the reduction in hippocampal activity in the suppress condition. The design of the experiment reported here represents two major departures from the standard TNT task that may underlie the failure to replicate this effect. First, in the current study several scenes were paired with only a small set of associates, unlike previous studies in which unique targets were used in each pair. This modification was made to permit exemplar-level decoding based on eye-tracking data. However, this may have discouraged participants from strongly suppressing the associate representation on a suppress or substitute trial, since the associate may need to be recalled in a subsequent trial in the retrieve condition. Second, unlike past studies, here each pair was presented only once. In the standard TNT task, participants complete anywhere between one and 16 repetitions of each pair in TNT phase. Indeed, below baseline forgetting is strongest for pairs that have been suppressed multiple times (Anderson & Green, 2001; Hotta & Kawaguchi, 2009; Hertel & Calcaterra, 2005; Anderson & Huddleston, 2012). Similarly, significant reduction of associate reinstatement only emerges at the fourth repetition of a no-think pair (Wimber et al., 2015). It is possible that a single attempt of suppression is not sufficient to downregulate hippocampal activity. These factors may have affected my ability in the current study to replicate previously demonstrated effects on hippocampal activity. It may be the case that hippocampal disengagement is only evident in trials in which participants have successfully suppressed their memories (i.e., after repeated attempts at suppression). Future analyses might examine whether this effect emerges in the current study on the subset of suppress trials in which participants dedicate low viewing to the associate of the scene cue (indexing successful suppression).

Another possibility is that the suppression-related hippocampal effect is small, and most evident for respective associate categories in subregions of the hippocampus and MTL involved in processing information from those categories. Past studies suggest that there is some selectivity in terms of the type of information processed in subregions of the MTL (e.g., higher face processing in the anterior portions of the hippocampus, Fairhall et al., 2014; Lee et al., 2008; greater object processing in the PrC, Litman et al., 2009; see Robin et al., 2018 for a meta-analysis). If it is the case that, for instance, suppressing faces selectively reduces activity in specific regions of the hippocampus involved in representing faces, then averaging across the entire hippocampus may obscure differences arising from associate categories. Future analyses might probe these subregions to examine whether a reduction in activity is more apparent in anatomically specific areas.

The aim of the current study was to examine the effect of memory regulation on associate reactivation specifically in the MTL. Past work examining memory reinstatement during retrieval has reported item- and context-specific reactivation in the MTL (Tompary et al., 2016; Mack & Preston, 2016; Dimsdale-Zucker et al., 2018). However, studies investigating memory regulation have largely limited multivariate analyses examining effects of regulation on reinstatement to regions of the brain involved in the sensory processing of the associate such as the parahippocampal gyrus (Meyer & Benoit, 2021; Detre et al., 2013) or the fusiform face area

(Detre et al., 2013). It is possible that reduction of reinstatement during memory control is more subtle in the MTL. In fact, Wimber et al. (2015) found that memory regulation reduced reactivation only in the inferior temporal cortex. This effect was not evident in the hippocampus. Further, forgetting of no-think items was correlated with the extent of pattern suppression in the inferior temporal cortex, but not in the hippocampus. Thus, including multivariate analyses in the current study from regions outside the MTL may be more informative in terms of elucidating the relationship between reinstatement, viewing behavior, and memory performance.

Conclusions

To conclude, in the current study, I developed a novel paradigm that paired eye-tracking with fMRI to address three open questions in the field of memory regulation. Overall, the results reveal that different strategies of memory regulation engage distinct cortical networks. Additionally, the current study contributes to the growing body of literature on memory regulation by demonstrating that the interactions between cognitive control mechanisms and memory retrieval can influence not just explicit recognition memory, but also more incidental measures such as eye-movement behavior.

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Appendix

Post-experimental Questionnaire

Please answer the following questions to indicate the extent to which you utilized each strategy when attempting to ***suppress*** items:

After the scene was presented I:

1. Made sure I still knew the associated face/tool first, and then tried to not think of this associated face/tool.

0	1	2	3	4
Never	Rarely	Sometimes	Frequently	Very frequently

2. Tried not to think of the associated face/tool, but then after the trial was over, I made sure I still remembered the associated face/tool.

0	1	2	3	4
Never	Rarely	Sometimes	Frequently	Very frequently

3. Kept myself from thinking about the associated face/tool by keeping my mind completely blank.

0	1	2	3	4
Never	Rarely	Sometimes	Frequently	Very frequently

Please answer the following questions to indicate the extent to which you utilized each strategy when attempting to ***substitute*** items:

After the scene was presented I:

1. Made sure I still knew the associated face/tool first, and then tried to call to mind a substitute tool/face.

0	1	2	3	4
Never	Rarely	Sometimes	Frequently	Very frequently

2. Tried not to think of the associated face/tool, and immediately called to mind a substitute tool/face.

0	1	2	3	4
Never	Rarely	Sometimes	Frequently	Very frequently

3. Always used the same face/tool for substitution (for example -- always used the *hammer* when trying to substitute for a face; always used *Obama* when trying to substitute for a tool).

0	1	2	3	4
Never	Rarely	Sometimes	Frequently	Very frequently

4. Made pairs between objects that I would use for substitution (for example -- always use the *hammer* when trying to substitute for Obama; always use *Rupert Grint* when trying to substitute for the scissors).

0	1	2	3	4
Never	Rarely	Sometimes	Frequently	Very frequently

Please answer the following questions to indicate the extent to which you utilized each strategy when attempting to ***retrieve*** items:

After the scene was presented I:

1. Made sure I still knew the associated face/tool first, and then kept it in mind until the search display was presented.

0	1	2	3	4
Never	Rarely	Sometimes	Frequently	Very frequently

2. Continued to try to retrieve the associate until the search display was presented if it did not immediately come to mind.

0	1	2	3	4
Never	Rarely	Sometimes	Frequently	Very frequently

3. Called the associated face/tool to mind, but then thought about something else until the search display was presented.

0	1	2	3	4
Never	Rarely	Sometimes	Frequently	Very frequently

Please answer the following questions to indicate the extent to which you performed the following behaviors ***when the search display was presented***:

After the search display was presented I:

1. Deliberately looked for (moved my eyes to) the associated face/tool in the search display on every trial (whether the instructions were to *retrieve, suppress, or substitute*).

0	1	2	3	4
Never	Rarely	Sometimes	Frequently	Very frequently

2. Deliberately avoided looking for (moving my eyes to) the associated face/tool in the search display regardless of trial type (whether instructions were to *retrieve, suppress, or substitute*).

0	1	2	3	4
Never	Rarely	Sometimes	Frequently	Very frequently

3. Deliberately looked for (moved my eyes to) the face/tool in the search display that I had used for substitution in the *Substitute* trials.

0	1	2	3	4
Never	Rarely	Sometimes	Frequently	Very frequently

4. Simply looked at the objects, without regard for whether they were associates, substitutes, etc. until the search target (the lone circle) was revealed.

0	1	2	3	4
Never	Rarely	Sometimes	Frequently	Very frequently

If you used a strategy during search that is not described above, please explain in the space provided below:

Curriculum Vitae

EDUCATION

Ph.D. Experimental Psychology (Neuroscience)
University of Wisconsin Milwaukee, USA, 2015 – Present
(Projected End date: June 2021)

M.Sc. Cognitive Neuroscience
University of York, UK, 2013 – 2014

B.A. Psychology
University of Pune, India, 2010 – 2013

RESEARCH PROJECTS

Neural Mechanisms of Long-term Memory Regulation

- Examine how memory suppression is accomplished by cognitive control mechanisms, and the effect of suppression on hippocampal reinstatement of retrieved memories
- Developed novel experimental paradigm to test memory regulation using fMRI and eye-tracking
- Coded task using proprietary eye-tracking software (SR Research)
- Currently in the process of collecting concurrent fMRI and eye-tracking data, analysing behavioral and eye-tracking data using R, and fMRI data using AFNI to measure neural mechanisms and consequences of memory regulation

Predicting Gist-Based False Memory Using Neural Pattern Similarity

- Investigate whether neural pattern similarity during encoding is predictive of performance on the DRM false memory task
- Compared the effect of multiple methods of modeling BOLD activity using AFNI on pattern similarity
- Conducted hippocampal hand-segmentations using ITK-SNAP
- Implementing ROI-based and searchlight Representational Similarity Analysis (RSA) analyses using R and pyMVPA to predict response accuracy

Contributions of Temporal Regularity to Long-term Memory

- Test whether temporal predictability during encoding improves learning
- Created novel stimulus set and conducted norming study
- Coded experiment in Presentation and collected behavioral data on three experiments
- Developed data analysis scripts in R to analyse behavioral and eye-tracking data
- Manuscript from the project is published in *Frontiers in Psychology*

Neural Topographic Maps as a Universal Substrate of Attention

- Test whether auditory attention is deployed through a map-like organisation in the parietal lobe
- Developed novel experimental paradigm to measure frequency-selective auditory attention using a sparse acquisition protocol developed for the 7T fMRI scanner in collaboration with researchers at the Medical College of Wisconsin
- Developed auditory stimuli and built experiment in Matlab using Psychtoolbox
- Collected fMRI data at the 7T scanner
- Processed high-resolution functional MRI data using custom Matlab and Python code

Effects of Music Training on Auditory Object Perception

- Examine how level of music training alters the processing of auditory information
- Used k-means clustering to develop a novel method of characterising level of music training
- Analysed behavioural responses using Principal Components Analyses to measure auditory object perception
- One manuscript from this project is in preparation with a targeted submission date of July 2021

Data Processing Pipeline for fMRI Data

- Developed scripts to simplify fMRI preprocessing in AFNI and Freesurfer in a BIDS-compliant manner
- Built tcsh module to streamline data reconstruction and pre-processing to be used across projects and labs
- Maintaining a (currently private) GitHub repository for this module

PUBLICATIONS

- **Kulkarni, M.** & Hannula, D. E. (2021). Temporal Regularity May Not Improve Memory for Item-Specific Detail. *Frontiers in Psychology, 12*, 1-11. https://doi.org/10.3389/fpsyg.2021.623402
- **Kulkarni, M.**, Potkonjak, K., Randall, R. & Greenberg, A. S. (in preparation). Formal music education alters perceived musicality of pitch sequences.

POSTERS

- **Kulkarni, M.**, Nickel, A. E., Hannula, D. E. (2021, March). Cognitive and Neural Correlates of Episodic Memory Regulation. Poster presented at the annual meeting of the Cognitive Neuroscience Society
- **Kulkarni, M.**, Hannula, D. E. (2020, November). Eye Movements are Sensitive to Episodic Memory Regulation. Poster presented at the annual meeting of the Psychonomic Society.
- **Kulkarni, M.**, Hannula, D. E. (2020, October). Temporal Regularity Does Not Improve Memory for Item-Specific Detail. Poster presented at the Expectation, Perception and Cognition Meeting.
- **Kulkarni, M.**, Hannula, D. E. (2019, November). Contributions of Temporal Expectation to Item-Specific Memory. Poster presented at the annual meeting of the Psychonomic Society, Montreal, QC, Canada.
- Mahoney, E. J., **Kulkarni, M.**, Hannula, D. E. (2018, April). Behavioural and Neural Markers of Memory Malingering. Poster presented at the annual Neuroscience Symposium at the University of Wisconsin Milwaukee, Milwaukee, WI.
- **Kulkarni, M.**, Huddleston, W. E., DeYoe, E. A., Greenberg, A. S. (2017, November). Topographic maps in attention control regions mediate frequency-based auditory attention. Poster presented at the annual meeting of Object Perception, Attention and Memory, Vancouver, BC, Canada
- **Kulkarni, M.**, Potkonjak, K., Randall, R. & Greenberg, A. S. (2015, November). Formal music education alters perceived musicality of pitch sequences. Poster presented at the annual Auditory Perception, Cognition and Action Meeting, Chicago, IL
- **Kulkarni, M.**, Garcia, R., Biddles, H., Giannakopoulou, E., Hymers, M., Millman, R. E. (2014, August). Functional Organisation of Familiar Melody Recognition. Poster presented at the annual Research Symposium at the University of York, UK.

TALKS

- **Kulkarni, M.**, Hannula, D. E. (2018, April). Contributions of Temporal Expectation to Item-Specific Memory. Talk presented at the annual research symposium of the Association of Graduate Students in Psychology at the University of Wisconsin Milwaukee, Milwaukee, WI.
- **Kulkarni, M.**, Huddleston, W. E., DeYoe, E. A. & Greenberg, A. S. (2017, October). Attendotonotopy: Frequency-based Priority Maps for Auditory Attention. Talk presented at the Neuroscience Seminar at the University of Wisconsin Milwaukee, Milwaukee, WI.
- **Kulkarni, M.**, Potkonjak, K., Randall, R. & Greenberg, A. S. (2016, November). Music Expertise Alters the Perception of Auditory Objects. Talk presented at the annual Auditory Perception, Cognition and Action Meeting, Boston, MA.
- **Kulkarni, M.** (2013, January). Jean-Jacques Rousseau: Implications of the General Will. Talk presented at the annual Philosophy Conference of S.P. College, Pune, India.
- **Kulkarni, M.** (2012, January). Jainism: Relationship between Spirituality and Morality. Paper presented at the annual Philosophy Conference of S.P. College, Pune, India.

TEACHING EXPERIENCE

- **Research Methods in Psychology:** TA Co-ordinator
  Instructors: Dr. Marcellus Merritt, Dr. Sue Lima
- **Research Methods in Psychology:** Teaching Assistant
  Instructors: Dr. Marcellus Merritt, Dr. Sue Lima, Dr. Peter Lenz
- **Physiological Psychology:** Teaching Assistant
  Instructor: Dr. Ira Driscoll

AWARDS AND ACHIEVEMENTS

- **Pilot Grant:** Center for Imaging Research, Medical College of Wisconsin
  November, 2019
- **Summer Research Fellowship:** University of Wisconsin Milwaukee
  Summer, 2017
- **First Position:** Talk presented at conference in S.P. College, Pune
  January, 2012

DEPARTMENT SERVICE

Secretary of Cognition, Learning, Attention and Memory (CLAM) Society

2017 – Present

- Co-wrote grants that received over $10,000 from UWM to support graduate student training, and conference travel
- Collaborated with graduate students to organize workshops on fMRI data analysis for UWM, Marquette University, and Medical College of Wisconsin students
- Hosted Dr. Bob Cox, Dr. Paul Taylor and Rick Reynolds for AFNI bootcamp at UWM

Psychology Day

2016 – Present

- Presented research at Department of Psychology undergraduate recruitment events
- Conducted research demonstrations at UWM booths at the Wisconsin State Fair

Graduate Student Ambassador for Department of Psychology, University of York

2013 – 2014

- Represented graduate student cohort at the department and university administrative meetings
- Organised end-of-the-year poster session for Masters students to showcase research

Undergraduate Mentoring

- Mentored several undergraduate research assistants on collecting and analysing behavioral and eye-tracking data

COMMUNITY ENGAGEMENT

Invited Community Talks

- Kulkarni, M., Blujus, J.K. (2019, July). It's all in the Brain: Neuroscience of Vision and Hearing. Talk given at Coffeeshop Astrophysics Meeting, Milwaukee, WI
- Kulkarni, M. (2018, April). Memory and the Brain. Talk given at BrainExpo 2018, Milwaukee, WI
- Kulkarni, M., Blujus, J.K., Fernandino, L. (2017, June). How are memories stored in the brain? Talk given at Coffeeshop Astrophysics Meeting, Milwaukee, WI

Volunteer at BrainExpo

2018 – Present

- Organized events aimed at educating general public about brain health and disease through interactive exhibits

- Conducted brain dissection demonstrations for elementary school children enrolled in the Montessori Brains program

Volunteer at Future Success Program
2018 – 2010

- Conducted workshops on data collection and analysis in Psychology for high-school students from minority backgrounds preparing for STEM undergraduate programs
- Developed and co-taught course on Python programming for high-school students interested in health sciences

SKILLS

- **Techniques:** Eye-tracking, fMRI
- **Programming:** R, Shell-scripting, Matlab, Python, High-performance computing
- **Stimulus Presentation Software:** Experiment Builder, Presentation, Psychtoolbox, PsychoPy
- **MRI Analysis Software:** AFNI, FSL, Freesurfer, ITK-SNAP, PyMVPA
- **fMRI and Statistical Analyses:** fMRI preprocessing, Whole-brain and ROI-based univariate analyses, RSA, MV