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Review

# Prefrontal–hippocampal pathways underlying inhibitory control over memory

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ABSTRACT

A key function of the prefrontal cortex is to support inhibitory control over behavior. It is widely believed that this function extends to stopping cognitive processes as well. Consistent with this, mounting evidence establishes the role of the right lateral prefrontal cortex in a clear case of cognitive control: retrieval suppression. Retrieval suppression refers to the ability to intentionally stop the retrieval process that arises when a reminder to a memory appears. Functional imaging data indicate that retrieval suppression involves top-down modulation of hippocampal activity by the dorsolateral prefrontal cortex, but the anatomical pathways supporting this inhibitory modulation remain unclear. Here we bridge this gap by integrating key findings about retrieval suppression observed through functional imaging with a detailed consideration of relevant anatomical pathways observed in non-human primates. Focusing selectively on the potential role of the anterior cingulate cortex, we develop two hypotheses about the pathways mediating interactions between lateral prefrontal cortex and the medial temporal lobes during suppression, and their cellular targets: the entorhinal gating hypothesis, and thalamo-hippocampal modulation via the nucleus reuniens. We hypothesize that whereas entorhinal gating is well situated to stop retrieval proactively, thalamo-hippocampal modulation may interrupt an ongoing act of retrieval reactively. Isolating the pathways that underlie retrieval suppression holds the potential to advance our understanding of a range of psychiatric disorders characterized by persistent intrusive thoughts. More broadly, an anatomical account of retrieval suppression would provide a key model system for understanding inhibitory control over cognition.


## 1. Introduction

Memories, like physical actions, sometimes need to be controlled. For example, although good memory for the past typically is welcomed, this feature poses a problem when memories are unpleasant and intrusive. When people encounter an unwelcome reminder, they strive to limit awareness of the unwanted memory by stopping its retrieval. This retrieval stopping process, known as retrieval suppression, is mediated by an inhibitory control mechanism that suppresses unwanted traces, rendering them less likely to be retrieved in the future (Anderson & Green, 2001; see Anderson & Hanslmayr, 2014; Anderson & Huddleston, 2011 for reviews). Over the last decade, evidence has grown showing that the brain systems underlying retrieval suppression exhibit important similarities and differences to other putative forms of inhibitory control, such as motor response stopping. Like motor stopping, retrieval suppression engages the right lateral prefrontal cortex; but, instead of modulating motor cortical regions, the prefrontal cortex suppresses hippocampal activity that supports retrieval (Anderson et al., 2004; Benoit & Anderson, 2012; Depue, Curran, & Banich, 2007; Depue, Orr, Smolker, Naaz, & Banich, 2015; Gagnepain, Henson, & Anderson, 2014; Levy & Anderson, 2012; Paz-Alonso, Bunge, Anderson, & Ghetti, 2013). These findings suggest that mnemonic functions of the hippocampus are subject to inhibitory control by the prefrontal cortex. If so, retrieval suppression may provide an important model system for studying inhibitory control over thought that complements and generalizes models of inhibitory control based on stopping action.

Whereas the anatomical pathways underlying action stopping are increasingly well characterized (e.g., see, e.g., Schmidt, Leventhal, Mallet, Chen, & Berke, 2013; for a review, see Aron, Robbins, & Poldrack, 2014), little is known about how the lateral prefrontal cortex modulates hippocampal activity to suppress retrieval. In this article, we begin to close this gap. In particular, we review anatomical findings observed with non-human

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primates that inform theories of how the prefrontal cortex could exert inhibitory control over hippocampal activity. In the first section, we describe key brain areas associated with retrieval suppression in human neuroimaging studies, and when they are observed. We then review what is known about interactions between DLPFC and the medial-temporal lobes (MTL) based on primate anatomical studies, and develop candidate pathways that could underlie mnemonic control. Focusing on the anterior cingulate cortex (ACC), we consider in detail the types of neurons to which ACC projects in MTL, and their regional and laminar distribution, with special attention given to their potential to regulate mnemonic activity. After developing candidate pathways, we discuss how well each fits the evidence, and the type of data needed to evaluate these hypotheses.

## 2. Suppressing memory retrieval by inhibitory control

A key premise of this article is that suppressing retrieval builds on prefrontally-mediated inhibitory control mechanisms similar to those engaged to stop motor actions. Consider an example of motor stopping. One evening, the first author accidentally knocked a potted plant off of his window sill. As his hand darted to catch the falling object, he realized that the plant was a cactus. Mere centimeters from it, he stopped himself from catching the cactus. This example illustrates how critical it can be to have the ability to override a strong reflexive response to a stimulus (Fig. 1). Like reflexive motor actions, environmental cues often trigger intrusive memories and thoughts that leap to mind, despite a desire to avoid them. These thoughts can be unpleasant when memories are unwanted. Given the tendency for environmental stimuli to elicit automatic motor or cognitive processes, some mechanism is required that can interrupt both types of processes, if we are to maintain voluntary control over actions and thoughts. Without the capacity to override unwanted processes, we could not adapt behavior or thoughts to changes in our goals or circumstances. The ability to stop is a fundamental function accomplished by inhibitory control, a mechanism believed to suppress representations that drive those processes, enabling the goal-directed interruption of behavior and thought. Of key concern here is how inhibitory control stops episodic memory retrieval when a cue begins to trigger a memory, a situation formally similar to motor stopping (Fig. 1).

### 2.1. Core behavioral findings

Retrieval suppression is often studied with the think/no-think paradigm (hereinafter, the TNT paradigm) (Anderson & Green, 2001). This procedure mimics situations in which we encounter a reminder to a memory we prefer not to think about, and try to keep the memory out of mind. To create reminders, participants study cue–target pairs (e.g., word pairs, or picture pairs; e.g., "ordeal roach") and are then trained to recall the second item (roach) of the pair whenever they encounter the first (ordeal) as a reminder. Participants then enter the think/no-think (TNT) phase, in which they are asked to exert control over retrieval. On each trial, a reminder from one of the pairs appears in green or red; when the reminder appears in green, participants are to recall the response; but for red reminders, participants are asked to suppress retrieval of the response, preventing it from entering awareness. The latter no-think task asks the participant to override the retrieval process and prevent the associated declarative memory from entering awareness despite the established tendency for the cue to elicit that memory. Participants are told that if the memory does come to mind during no-think trials, they are to suppress it. The key question concerns whether people can recruit inhibition to overcome memory intrusions by learning to prevent the memory from intruding into consciousness, and whether doing so disrupts later retention of the excluded memory. To measure the disruptive aftereffects of retrieval suppression, participants receive a final test in which they are given each reminder and are asked to recall the associated response. Memory performance is compared between items that participants suppressed (No-think trials), items that they retrieved (Think trials), and items that they studied, but neither suppressed nor retrieved during the TNT phase (Baseline trials). Comparing final recall of No-Think items to either Think or Baseline items indicates whether retrieval suppression has a detrimental effect on retention.

The TNT procedure consistently shows that people can stop the retrieval process. This conclusion receives support from several notable effects. First, retrieval suppression abolishes the benefits of reminders on memory, as revealed by the often substantial difference in final retention between Think and No-Think items. Indeed, many studies show that reminders to No-Think items can be presented over a dozen times with little apparent benefit in accessibility of the associated traces. Thus, at a minimum, suppressing retrieval reduces the facilitation that retrieved memories usually enjoy. Second, suppressing retrieval often reduces recall for No-Think items below that observed for Baseline items, a phenomenon known as *suppression-induced forgetting*. Suppression-induced forgetting is especially informative because it indicates that during retrieval suppression, reminders do not merely fail to enhance retention, they trigger processes that impair voluntary access to the unwanted memory. Third, the impairment of the excluded memory occurs even when it is tested with a novel cue, indicating a generalized impairment of the trace, consistent with the idea that the memory has been inhibited. Most of these effects have been observed with both verbal cue–target pairs and visual pairs such as face–scene pairs, and the effects arise for target items with emotional content (see Anderson & Hanslmayr, 2014, for a review). Thus, stopping unwanted retrievals appears to be achieved in part by suppressing the associated memory, consistent with inhibitory control. As such, the TNT paradigm provides a model for studying inhibitory control over memory that parallels procedures used to study motor response suppression.

Suppression-induced forgetting shows that suppressing retrieval impairs people's ability to intentionally recall previously suppressed traces. In real world cases of memory control, however, people are rarely motivated to retrieve purposefully the very memories that they have previously suppressed; rather, people are more concerned with stopping the tendency for unwanted memories to intrude involuntarily. A better estimate of the true impact of inhibition on spontaneous retrieval patterns would assess the *tendency* for memories to come to mind involuntarily, not people's *ability* to retrieve them. Research on retrieval suppression indicates that the impact of inhibitory control on involuntary retrievals is even more substantial than its effect on voluntary retrieval. One way that this has been studied is by asking people, after each No-Think trial, whether the unwanted memory came to mind, despite their efforts to stop it from doing so. Remarkably, whereas intrusive memories are extremely common on early suppression trials (often around 60% of trials), they become progressively less common in later suppression trials, showing proportional reductions of nearly 50% (see, e.g., Levy & Anderson, 2012; Benoit, Hulbert, Huddleston, & Anderson, 2015). The effectiveness of reducing involuntary retrievals predicts later suppression-induced forgetting effects, indicating that a common mechanism underlies these phenomena (Levy & Anderson, 2012). These findings suggest that engaging inhibitory control to suppress involuntary retrievals ought to have a substantial impact on spontaneous retrieval patterns in daily life, a possibility consistent with reports of relatively large suppression-induced forgetting effects on free