Brain Mechanisms Underlying the Inhibitory Control of Thought

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Controlling action and thought requires the capacity to stop mental processes. Over the last two decades, evidence has grown that a domain-general inhibitory control mechanism supported by the right lateral prefrontal cortex achieves these functions. However, current views of the neural mechanisms of inhibitory control derive largely from research into the stopping of action. Whereas action stopping is a convenient empirical model, it does not invoke thought inhibition and cannot identify its unique features. Here we review research using a different model of inhibitory control that addresses how organisms stop a key process driving thoughts: memory retrieval. Retrieval stopping shares right anterior dorsolateral and ventrolateral prefrontal mechanisms with action stopping, consistent with a domain general inhibitory control mechanism; however, retrieval stopping also recruits a distinct fronto-temporal pathway that determines mental control's success. For example, GABAergic inhibitory networks within the hippocampus, driven polysynaptically by prefrontal input uniquely contribute to thought suppression. These unique elements of mental control raise the hypothesis that hippocampal disinhibition is a transdiagnostic factor underlying intrusive thinking, linking the proposed fronto-temporal inhibitory control pathway to preclinical models of psychiatric disorders and to fear extinction. We suggest that transdiagnostic retrieval-stopping deficits underpin broad vulnerability to psychiatric disorders and are reflected in robust aberrations in large-scale brain network dynamics.

Introduction

Intelligence requires the capacity to control cognition. Such control would be impossible without the ability to stop thoughts. Over recent decades, the discussion about the cognitive and brain systems involved in cognitive inhibition and its disorders often has built on the study of how organisms stop physical actions[1–5]. By this approach, stopping a simple action such as a finger or eye movement, provides a vital proxy for the broader ability to stop unwanted mental processes. Studying action stopping has clear virtues: physical actions are objectively expressed, and so their stopping is readily witnessed in humans or in animals; and formal theoretical frameworks and measurement models enable precise quantification of stopping speed[5–8]. This historical focus on action stopping has spawned a voluminous literature on inhibitory control– a putative mechanism that suppresses representations or processes that conflict with our current goals[2,9,10]. This multifaceted literature offers the comfort of convergent evidence about the role of fronto-subthalamic circuitry, drawing from functional brain imaging, intracranial recording, brain stimulation, animal models, lesion studies, and computational modelling[2,11]. Despite these virtues, action stopping's limits as a model system for other types of inhibitory control receive less attention. Is action inhibition the best model for understanding thought stopping? Could stopping a finger movement or saccade when signaled to do so truly reveal the origins of intrusive memories in post-traumatic stress disorder, pathological worry in anxiety, rumination in depression, and obsessive thinking in obsessive compulsive disorder?

In this article, we review research using an alternative model system for inhibitory control that directly addresses how thoughts are stopped: retrieval stopping. In retrieval stopping, one confronts a reminder associated to an experience or thought that one prefers (or is instructed) not to think about. In response, one seeks to stop the reminder from eliciting the associated thought. Thus, retrieval stopping, like action stopping, engages inhibitory control to target a process triggered by an imperative stimulus. Unlike action stopping, however, inhibitory control targets the retrieval process generating unwelcome memory content instead of an unwelcome motor response. Action and retrieval stopping both engage the right lateral prefrontal cortex, consistent with a domain-general stopping mechanism. Importantly, however, the brain regions that are modulated during retrieval stopping (and the pathways that achieve modulation) differ from those modulated by action inhibition. Thus, whereas action stopping cap-

tures the prefrontal cortex's role in inhibitory control, it omits downstream domain-specific components critical to thought stopping. Such omissions impede the use of action stopping to understand psychiatric symptoms thought to reflect deficient inhibitory control.

To highlight the substantially different mechanisms underlying the inhibitory control of thought, we introduce the term *fronto-temporal inhibitory control pathway* to summarize its main features. We illustrate how identifying factors unique to this fronto-temporal pathway forges novel connections between animal models of anxiety, depression, and affect regulation, integrating disparate literatures relevant to disordered thought control.

Here we argue that suppressing unwanted thoughts and emotions may be conceptualized as retrieval stopping via the fronto-temporal inhibitory control pathway. We first illustrate how controlling retrieval engages inhibitory control, focusing in depth on retrieval stopping as a model case (mnemonic inhibitory control during selective retrieval (e.g., [12]) and working memory updating (e.g., [13]) lie outside this review). We then review research on what retrieval stopping reveals about how people achieve control over intrusive thoughts. We suggest that an in-depth model of inhibitory control over memory better positions neuroscience to isolate the pathogenesis and pathophysiology of intrusive cognition in psychiatric disorders. This framework for inhibitory control over thought is well-suited to the development of innovative interventions tailored to psychiatric conditions associated with disordered thought control.

Retrieval Stopping and the Control of Thought

To illustrate why stopping actions and thoughts might call upon similar mechanisms, consider an example of motor stopping. One evening, the first author knocked a potted plant off of his windowsill. As his hand darted to catch the falling plant, he realized that it was a cactus. Mere centimeters from it, he stopped himself from catching the cactus. Thus, a stimulus triggered a reflexive response, which, while usually appropriate, needed to be stopped. This example highlights why the ability to cancel a strong reflexive response to a stimulus can be critical in adjusting behavior. Like reflexive actions, stimuli often activate thoughts and memories that leap to mind involuntarily[14–17]. Yet, automatically retrieving ideas, images, or memories, while useful, sometimes undermines our focus or emotional state (Fig. 1a). Given that stimuli often automatically elicit motor or cognitive processes, organisms require a mechanism for stopping both types of process, to control behavior and thought. Stopping an initiated action is thought to be achieved by inhibitory control[5,6,9,18], a mechanism that actively suppresses representations or processes (Fig. 1b). Thus, stopping demands unite the regulation of action and thought via inhibitory control[19].

Although controlling thought often entails stopping, the stopping process acts on memories being retrieved, not on actions. According to this retrieval stopping view, content emerging in awareness in response to cues reflects the reactivation of representations associated to those cues. Whether those representations constitute past experiences, mental images in different modalities or semantic concepts, and whether they concern the past or the future, or timeless ideas, cues drive content to emerge; and ceasing awareness of content entails suppressing the retrieval machinery or the representations that retrieval produces. Evidence indicates that similar large-scale brain networks govern these types of retrieval[20,21], raising the prospect that a general retrieval stopping mechanism suppresses diverse thought content. Critically, because the processes and representations targeted by retrieval stopping must differ from action stopping (by content), the downstream mechanisms, anatomical pathways, and the impacts of inhibitory control beyond the prefrontal cortex require further study to understand thought control deficits in psychiatric disorders (Fig. 1c).

Retrieval Stopping: Behavioral Findings

Much of what has been learned about retrieval stopping has been observed with the Think/No-Think procedure (hereinafter, TNT procedure[22] Fig. 2; see[23] for a detailed methodological guide). Action stopping tasks such as the classical Stop-Signal tasks inspired this procedure's structure. The TNT procedure models situations in which we encounter a reminder to a memory that we prefer not to think about and then try to stop remembering it. To create reminders, participants study cue–target pairs (e.g., word or picture pairs) and are then trained to recall the second item upon seeing the first. Participants then enter the critical Think/No-Think (TNT) phase. On each trial, a pair's reminder appears; for some cues, participants must recall the associated item, whereas for others, they must prevent its retrieval. Participants can receive two varieties of instruction concerning how to prevent retrieval: Direct suppression and Thought Substitution[24–26]. Direct Suppression instructions ask participants to simply stop retrieval without generating distracting thoughts during the cue; and any memories that come to mind anyway are to be immediately excluded from awareness. Thus, participants encounter stimuli that elicit an automatic response (a memory instead of an action) and must stop that response (retrieval), modeling the stopping of unwanted thoughts. In contrast, Thought Substitution instructions ask participants to use the reminder to generate alternative thoughts (e.g., to retrieve a non-specific distractor memory or a pre-learned item). Thought substitution requires selective cancellation of one memory retrieval, and the enhancement of another, paralleling the demands of selective stopping in response inhibition studies[27–30]. These two instructions thus differ in whether they discourage an internal state that facilitates retrieval (retrieval mode), or instead encourage retrieval, but of alternate thought content[31]. Their neural mechanisms substantially differ[32]. Here, we focus on research using Direct Suppression, given its parallels with action cancellation.

The TNT task tests whether people recruit inhibition to overcome intrusions of an unwanted item and whether

Figure 1. Retrieval stopping as a model for inhibitory control over thought. a, Stimuli often evoke distressing memories that people are motivated to stop, such as when someone sees a car resembling the one in which they had a terrible accident. **b**, The canonical retrieval stopping situation. People can reduce awareness of unwanted thoughts by stopping the retrieval of a memory (faded circle) triggered by reminders in working memory (dotted box). During retrieval cancellation, pattern completion processes that drive the progression from cues to the associated memory are interrupted by inhibitory control processes that suppress the unwelcome content (represented by whited out memory). **c**, Transdiagnostic relevance of retrieval stopping to intrusive thinking across psychiatric disorders. Psychiatric symptoms such as intrusive memories, pathological worry, rumination, obsessive thinking, and cravings share similarities that can be understood as difficulties with retrieval stopping. In each case, intruding thought content is involuntarily retrieved, evoked by cues in the person's external or internal environment. Intrusions may be of past experiences (as in PTSD), or imagined scenarios (e.g., fearful imagery, imagined arguments, drug-taking thoughts) likely to be represented in part via hippocampal traces. Retrieval stopping thus may be a transdiagnostic process central to understanding perseverative cognition.

doing so disrupts the excluded thought. To measure suppression's disruptive effects, participants complete a cued recall test for all studied items after the TNT phase (Fig. 2a). Performance is compared between suppressed items (No-Think items), retrieved items (Think items) and items that were neither suppressed nor retrieved during the TNT phase (Baseline items). Several effects indicate that people can stop retrieval. First, retrieval stopping prevents reminders from benefitting memory; whereas repeatedly cuing Think items facilitates their later retention on delayed tests, relative to Baseline items (Panel 2C, left halves), No-Think items enjoy no such benefit of repeated reminders. Thus, stopping retrieval attenuates the memory improvement that reminders usually promote, limiting the integration of unwanted experiences into memory. Second, suppressing retrieval often reduces No-Think item recall below that of Baseline items, a phenomenon known as *suppression-induced forgetting* (SIF; Fig. 2c, right halves of panels). SIF indicates that during retrieval stopping, reminders trigger mechanisms that diminish the suppressed thought's accessibility. Third, SIF occurs even when testing the suppressed thought with a novel cue, indicating its generalized impairment (Fig. 2c). This "cue-independence" suggests that retrieval stopping induces forgetting that is not primarily associative, as its occurrence often does not depend on a particular cue[22] (though associative components can contribute[34]). Although most studies test recent associations, SIF also occurs for one-week old consolidated memories[35]. Most forgetting effects arise with both verbal and visual cue–target pairs (e.g., face–scene associations), but suppression also impairs memory for motor sequences[36] and videos[37,38]. The effects occur for unpleasant items[32,39–42] but also rewarding content, including images of addictive substances[43]. SIF has also been observed with autobiographical memories[44–46]. Thus, stopping retrieval suppresses the associated memory[47].

Importantly, stopping retrieval also gradually reduces a memory's tendency to intrude in response to reminders, limiting its power to distract[15,33,48–54] (Figures 2b and 2d). Retrieval stopping reduces the suppressed content's influence on unconscious expressions of memory[55] including perceptually-driven tests such as perceptual identification[51,56,57] and conceptually-driven tasks that measure accessibility of ideas underlying the suppressed item[44,58–61]. The disruptive impacts of retrieval stopping and other forms of memory inhibition can even be observed indi-

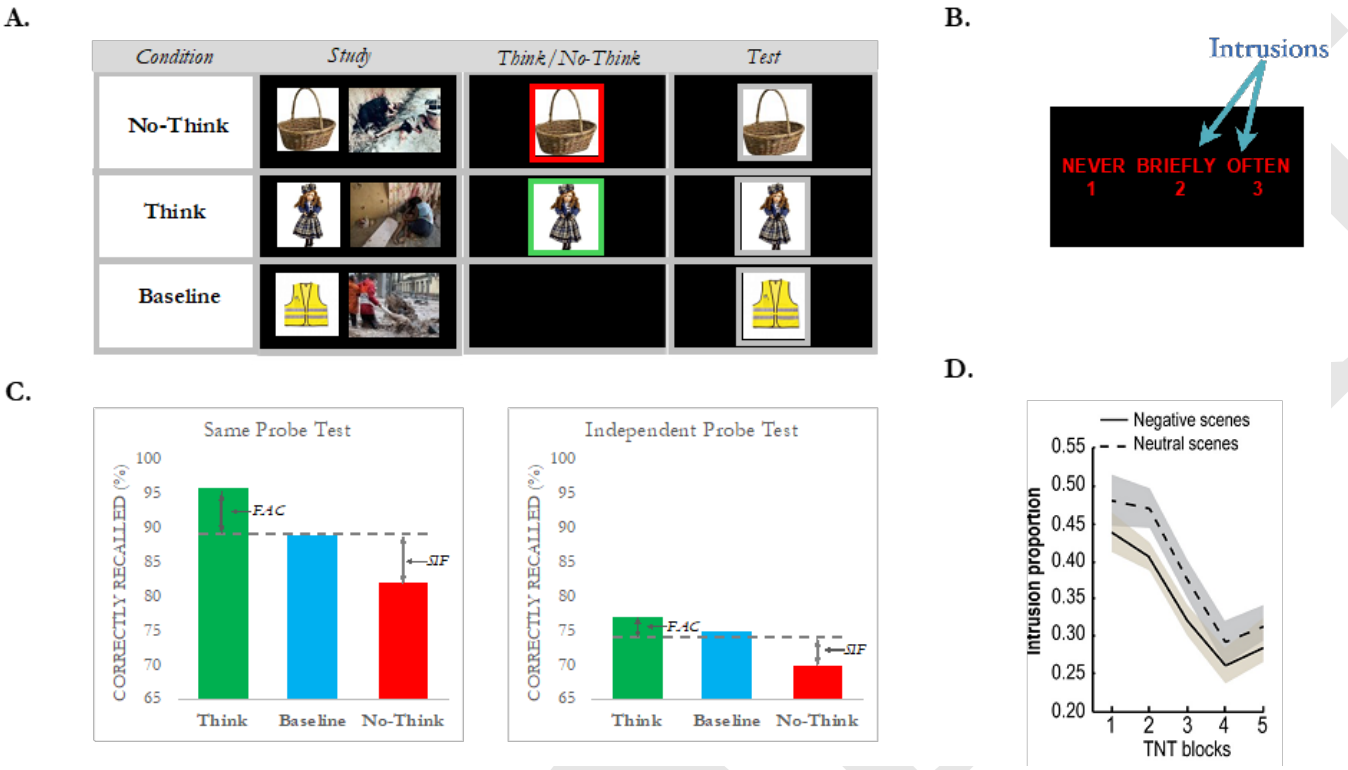


Figure 2. Retrieval stopping methods and representative behaviour. a, The Think/No-Think (TNT) procedure involves 3 phases: study/learning, TNT, and final test. After studying paired-associates (left column), participants are trained to recall the righthand items when cued with their reminders. The TNT phase (middle column) presents 3-second trials displaying a reminder bounded by a red or a green box (No-Think and Think trials, respectively). On No-Think trials, participants attend the reminder, but prevent the associated item from entering awareness; on Think (green) trials, participants attend the reminder while covertly recalling the item. No-Think and Think items are consistently suppressed or retrieved (usually across 8-12 repetitions). On the final test (right column), participants are cued to recall the No-Think (top row), Think (middle row) and Baseline (bottom row) scenes. **b**, During the TNT phase, some studies include trial-by-trial intrusion reports, probing whether the item entered awareness during the trial (never, briefly, or often). **c**, Typical final performance on two recall tests: the Same-Probe (usually given) and Independent Probe tests (sometimes given). Suppression-induced forgetting (SIF) refers to worse memory for No-Think, compared to Baseline items (right halves of panels, vertical line); facilitation (FAC) refers to improved memory for Think, relative to Baseline items (left halves of panels, vertical line). The Independent-probe test tests participants with different cues than those used to train suppression, establishing that forgetting generalizes over cues (cue-independence), an indicator of memory inhibition. **d**, Intrusion reports collected during the TNT task typically indicate increasingly effective control of awareness over blocks (data from[33]). In imaging studies, intrusion reports can be used to isolate activations triggered by intrusions and their regulation.

rectly in eye movement indices of memory[62–64].Together, retrieval stopping's impact on explicit memory, intrusiveness, and implicit memory implicates that suppressed content is inhibited, consistent with inhibitory control.

Inhibitory Control Mechanisms in Retrieval Stopping

Imaging studies have documented the brain systems engaged during retrieval stopping, the areas that these systems modulate, and their dynamic interaction that produces SIF. Here we review the prefrontal cortex's role in retrieval stopping, along with a broader network, and this network's resemblance to that involved in motor stopping. We then describe regions showing reduced activation during retrieval stopping, and evidence for medial-temporal targeting of inhibitory control.

Modality-General Prefrontal Mechanisms

Suppressing unwanted thoughts elicited by reminders engages a right-lateralized fronto-parietal control response. Specifically, fMRI studies reveal that stopping retrieval engages the right dorsolateral prefrontal cortex (DLPFC), right ventrolateral prefrontal cortex (rVLPFC) and bilateral insula, with dorsal anterior cingulate cortex (dACC), pre-supplementary motor area (pre-SMA), and bilateral angular/supramarginal gyrus. Right DLPFC activations often extend along the full anterior-posterior length of the middle frontal gyrus. However, DLPFC activations in an anterior BA9/46/10 area (hereinafter referred to as aDLPFC) appear especially important to inhibitory control, as discussed shortly. This right DLPFC/VLPFC control response occurs during the suppression of diverse content, irrespective of valence, including neutral and negative words[15,24,65–70], neutral visual objects[33,51], faces[48], neutral and aversive scenes[33,48,71–75], and unpleasant autobiographical memories[46]. Right VLPFC and aDLPFC also may contribute to cognitive operations involved in suppressing working memory contents[13,76–82], successful item-method directed forgetting[83,84] and thought suppression in the white bear paradigm[85,86]. However, avoiding retrieval of No-Think targets by retrieving distracting thoughts, pri-

marily engages *left* VLPFC, dissociating thought substitution from retrieval stopping[24].

Thought stopping poses neurocognitive demands resembling those present when we stop actions (Fig. 3a). Indeed, comparisons of thought and action stopping reveal co-localized activations in many of the foregoing thought stopping regions. For example, Apšvalka et al.[68] had participants perform alternating blocks of the Think/No-Think and Stop-Signal tasks, using neutral word pairs and visual-manual associations, respectively. A within-participants conjunction analysis on these tasks' stopping contrasts revealed right aDLPFC (spanning BA 9/46/10), rVLPFC (BA 44/45) and insula activations, together with right supramarginal/angular gyrus (Fig. 3b, red). A companion meta-analysis of 40 Stop-Signal and 16 Think/No-Think studies converged with the within-subjects comparison, with the conjunction of the meta-analytic inhibition contrasts for these domains yielding similar regions (Fig. 3b, blue, yellow). Depue et al.[72] also compared action and retrieval stopping within-subjects: both engaged right aDLPFC, although rVLPFC only arose for action stopping. A meta-analysis of imaging studies revealed that right aDLPFC and VLPFC's function extends to stopping reflexive eye movements (anti-saccade task), converging with lesion evidence[87–89] for their causal role in stopping. Together, these findings support roles for both right aDLPFC and rVLPFC in domain-general inhibitory control, with the former potentially playing an especially important role as demands on reactive inhibitory control increase[90]. Importantly, domain-general aDLPFC stopping activations and their accompanying cortical network are sometimes adjacent to, but distinct from the widely studied multiple-demand control network[91], with modest overlap in some areas (Fig. 3b; see[92] for converging evidence) and greater cingulo-opercular network engagement[68,92]. This activation profile also establishes that the historically diverging emphases on rVLPFC and right aDLPFC in action[9] and retrieval stopping[24] research were overly selective, as both regions contribute across both domains[11,68]. The regional activation similarity of the TNT and Stop-Signal tasks extends to the basal ganglia (Fig. 3b, lower), wherein co-localized stopping activations in the right caudate/putamen and the globus pallidus have been documented meta-analytically[93]. Thus, the fronto-striatal interactions thought crucial for stopping actions also likely occur during thought stopping[94].

Right aDLPFC and VLPFC support successful stopping behavior in both action and thought domains. For example, Apšvalka found that activity in the domain-general regions from their meta-analytic conjunction analysis predicted action and thought stopping efficiency. Behavioural partial-least squares analysis revealed a latent factor in which activation patterns across voxels in aDLPFC and VLPFC predicted individual variation in thought stopping (as SIF) and action stopping (as SSRT), with higher activity predicting faster stopping and superior forgetting. Thus, suppressing unwanted thoughts may rely on prefrontal mechanisms that support action stopping ability. Consistent with this, there have been reports of SIF's associations with SSRT[68,96,97], electrophysiological stopping signatures, such as the N2[98,99], attentional control measures[100,101], non-invasive executive control markers (e.g., heart-rate variability[49,102]) as well as enhanced SIF when people concurrently sustain physiological inhibition[103]. Associations between action and thought stopping indices do not always arise, however[95], suggesting that domain-specific factors also contribute to behavioural expressions of control success. Analogous correlations also have been found between Stop-Signal reaction time and intentional forgetting in the item-method directed forgetting procedure[104], which also recruits both aDLPFC and VLPFC[84,105]. Critically, in a large sample, greater cortical thickness and surface area in right aDLPFC predicted higher scores on a latent variable estimate of a task-general component of executive function (Fig. 3d)[106] –a component that may itself reflect inhibitory control[107]. Notably, the right aDLPFC is more anterior than expected by proposals positing a central role of mid-DLPFC to cognitive control[108].

Co-localized rDLPFC and rVLPFC activations for action and retrieval stopping provide promising evidence for a general stopping process, but other interpretations exist. Such activations could instead reflect different computations that are interdigitated. If so, multivariate activation patterns across voxels may differ across domains. Cross-task decoding findings provide evidence against this possibility. Apšvalka et al.[68] found that the activation patterns within the right aDLPFC and VLPFC during thought suppression resembled action stopping sufficiently that a classifier trained on action stopping could decode whether a person was suppressing a thought (and vice versa) (Fig. 3c) and could predict SIF. Domain-general angular/supramarginal gyrus regions yielded similar results. Critically, however, action and thought stopping also differed: classifiers were readily trained to distinguish action and thought stopping, showing that each has unique features as well. Apšvalka et al. argued that distinct features inevitably arise from the need for thought and action stopping to receive input from different cortical regions (input features) and effectuate output to differing target sites (output features).

Right aDLPFC and VLPFC also contribute to stopping emotional responses. Emotion regulation engages left and right lateral prefrontal cortices[109–112], with right DLPFC involvement clearest during emotional distancing strategies[109,110]. Interestingly, an affective stopping process (as distancing might require) recruits the foregoing domain-general stopping regions. For example, Depue et al.[72] compared, within subjects, brain regions involved in stopping retrieval, actions, or emotions, using the Think/No-Think, Stop-Signal, and Emotion Stopping tasks, respectively. The Emotion Stopping procedure required participants to view aversive scenes and either (a) feel the emotion suggested by the scenes or (b) detach themselves from emotional responses. Afterwards, participants rated the Detach scenes as less upsetting, relative to the Feel scenes, but also to aversive Baseline scenes not previously encountered. This

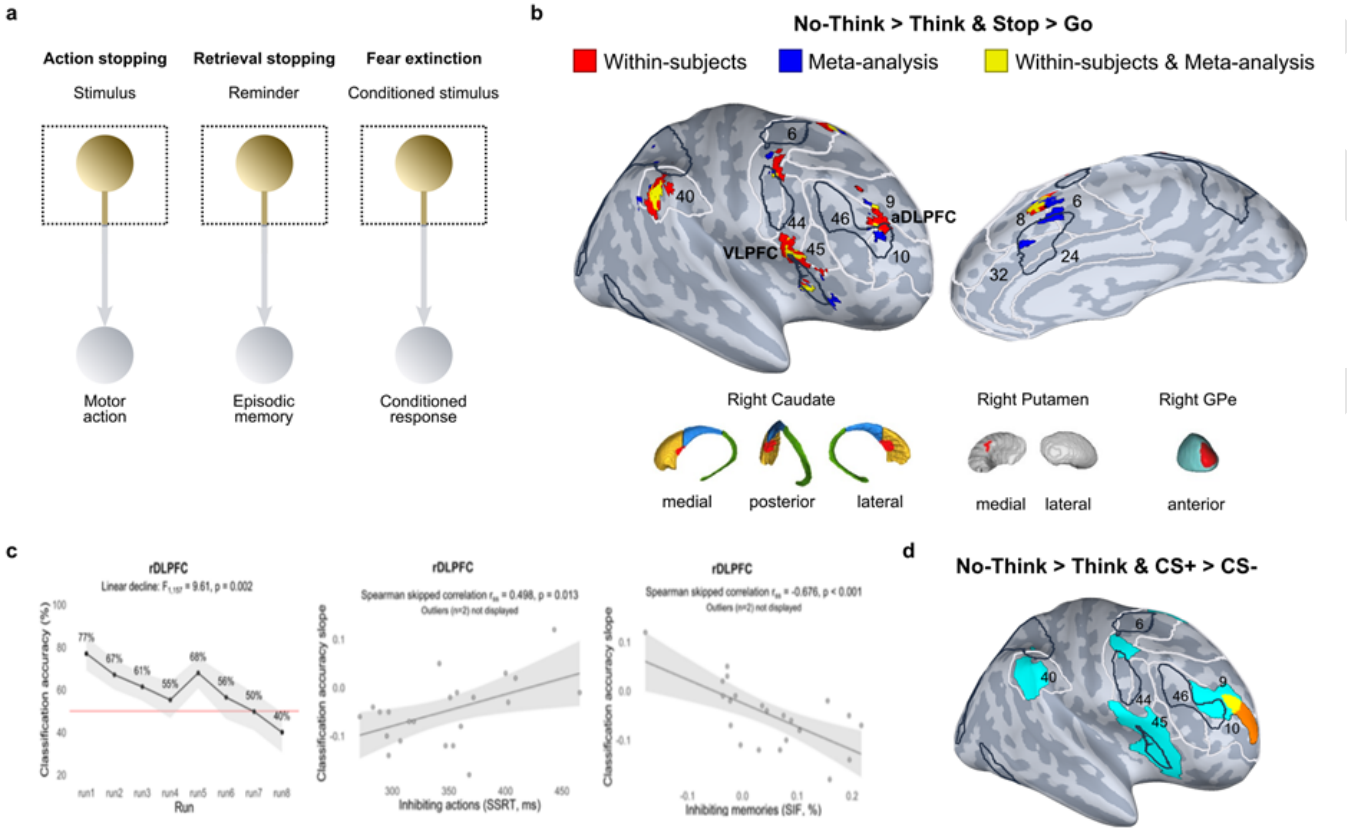


Figure 3. Domain-general prefrontal components of inhibitory control. a, Functional similarities between stopping action, retrieval, and affect. In each case, an attended stimulus enters working memory (dotted box), driving retrieval of an associated item (an action representation, an episodic memory, or a conditioned emotional response), which the organism stops via a domain-general inhibitory control process that suppresses it (represented by whited out areas). **b**, Domain-general stopping activations[68]. Red: within-subjects (N = 24) conjunction of the Stop > Go (action stopping) and the No-Think > Think contrasts thresholded at p < 0.05 FDR corrected for whole-brain multiple comparisons. Blue: meta-analytic conjunction of Stop > Go and the No-Think > Think contrasts from 40 Stop-Signal and 16 Think/No-Think studies using GingerALE. Yellow: overlap of the within-subjects and meta-analytic conjunctions. For comparison, black-outlined areas represent the multiple-demand system[91]. Results are displayed on an inflated MNI-152 surface with white-outlined and numbered Brodmann areas. aDLPFC = anterior dorsolateral prefrontal cortex; VLPFC = ventrolateral prefrontal cortex. Lower in panel b: Meta-analysis of basal ganglia activations shared by action and retrieval stopping (Guo et al.[93]). **c**, Using right aDLPFC activations, a classifier trained to distinguish Stop and Go trials in theStop-Signal action stopping task could distinguish No-Think and Think trials overall; however, classification accuracy declined significantly as participants suppressed the same thoughts repeatedly over runs. This decline suggests that inhibitory control grows less necessary as suppression induces forgetting and thoughts grow less intrusive. Faster Stop-Signal reaction times (better inhibition ability) predicted steeper declines in classification across runs (middle panel) as did superior suppression-induced forgetting (right panel). **d**, Meta-analytic conjunction of extinction learning (CS+ > CS- from 41 studies; CS+ = conditioned stimulus; CS- = control stimulus) and retrieval stopping (No-Think >Think from 22 studies) (N = 2475) using seed-based D-mapping, indicates that stopping fear engages regions recruited by retrieval stopping. This domain-general stopping region overlaps with a region showing a correlation of cortical thickness and task-general executive functions[95]. The overlap with extinction remained using only TNT studies employing neutrally-valenced pairs suggesting that shared activations reflect memory control, not affective content. Cyan: meta-analytic conjunction of CS+ > CS and the No-Think > Think contrasts. Orange: correlation between cortical thickness and task-general executive funtction. Yellow: overlap of the meta-analytic conjunction and correlation. Black-outlined areas represent the multiple-demand system.

affective inhibition correlated with SIF in their TNT task. Importantly, mnemonic, motoric, and affective stopping all engaged the right aDLPFC. Echoing this pattern, a meta-analysis found that fear extinction engages the right aDLPFC and VLPFC regions involved in domain-general stopping (see[113]; Fig. 3d). Fear extinction, though often viewed as passive, may engage inhibitory control to suppress memory and affect, based on the retrieval stopping model of fear extinction[114]. Thus, the right aDLPFC and VLPFC stopping function may span mnemonic, affective, and action domains (Fig. 3a), a possibility that extends to the networks in which they participate[68,93,115,116]. The importance of these prefrontal mechanisms to mnemonic and affective stopping highlights their likely relevance to PTSD and other psychiatric disorders.

Electrophysiological studies also support a domain-general inhibitory mechanism. This work builds on the discovery of beta-band activity as a response inhibition mechanism (beta-band includes events and oscillations in the 15-30 Hz range). Using the Stop-Signal method, intracranial electroencephalography (EEG) recorded from the rVLPFC reveals that increased beta-band power (16 Hz) distinguishes successful vs. failed action stopping, initiating a cascade of beta bursts in subthalamic nucleus and tha-

lamic structures implementing response inhibition[117,118]. This activity emerges within the time window of the stopping process inferred by the Stop-Signal procedure[119,120]. A similar signature occurs in source-resolved scalp EEG[121]. Building on this marker, Castiglione et al.[97] found that action (Stop-Signal) and thought stopping (TNT) elicited right frontal -band signals, with the beta effect greater on trials when intrusions had been prevented. Relatedly, Hubbard and Sahakian[104] probed for inhibitory control's role in item-method directed forgetting using scalp electrophysiological activity. Cross-task decoding revealed that frontal -band activity arose during action-stopping and memory inhibition. Moreover, classifiers trained to discriminate successful stopping discriminated successful forgetting of to-be-forgotten material. Action stopping indices (SSRT) and frontal beta power during action stopping also correlated with directed forgetting. Importantly, simultaneous fMRI/EEG during retrieval-stopping[66] and intracranial EEG during item-method directed forgetting[105] tie -band activity originating in the rDLPFC to hippocampal regulation.

Although the preceding findings reveal prefrontal mechanisms key to action and thought stopping, they do not specify how diverse content is controlled. To achieve generality, an inhibition mechanism must engage a cognitive control hub[122] capable of modulating diverse cortical and subcortical regions representing the content, in a goal-dependent manner. Critically, to constitute inhibitory control, this process should suppress targeted regions, degrading their functions temporarily. Although fundamental to domain-general inhibitory control, little work evaluates whether any prefrontal region exhibits this characteristic, which Apšvalka et al.[68] refer to as *dynamic inhibitory targeting*. Depue[72] reported early evidence for this possibility: Seed-based connectivity revealed that the same right aDLPFC region was associated with hippocampus during retrieval stopping and the amygdala, during emotion stopping. Such evidence, however, does not permit inferences about causality. Recently, Apšvalka[68] reported effective connectivity evidence (dynamic causal modelling) of dynamic targeting. Apšvalka found that right aDLPFC and VLPFC jointly modulated either motor cortical or hippocampal activity, depending on the task goal: whereas they modulated M1 during action stopping, they modulated hippocampus during retrieval stopping (Fig. 4a). Dynamic causal models involving both prefrontal regions robustly outperformed models involving only aDLPFC or VLPFC. Indeed, aDLPFC and VLPFC showed strong evidence of bidirectionally interacting during action and thought stopping, suggesting integrated action.

Together, these findings indicate that right aDLPFC and VLPFC exhibit characteristics needed by a domain-general inhibitory control mechanism: co-localized stopping activations across several domains, behavioural relevance to action and thought stopping performance, and dynamic targeting of content-specific regions that are putative targets of control. Critically, however, they reveal that despite sharing domain-general prefrontal mechanisms with action and affective stopping, thought suppression arises via a distinct *fronto-temporal mnemonic inhibitory control pathway*. Next, we turn to evidence for the inhibitory nature of hippocampal modulation.

Hippocampal Modulation Suppresses Thoughts

Inhibitory control's downstream impact necessarily differs for action and thought stopping. Most action stopping studies ask people to stop button-presses which recruit motor effector neurons in area M1. Most retrieval stopping studies, however, involve suppressing recently presented content, such as words or pictures associated to cues. A large imaging literature indicates the hippocampus's importance to episodic retrieval[123,124]. Correspondingly, whereas the prefrontal cortex modulates motor cortex during action stopping[124], it should modulate the medial temporal lobes during thought suppression. Apšvalka et al.[68] confirmed these differing impacts. Using alternating action and thought stopping mini-blocks, Apšvalka doubly dissociated the suppressive effects of retrieval and action stopping on the hippocampus and M1 (Fig. 4b) respectively. Thus, the regions targeted by inhibitory control change in a goal-dependent manner.

During retrieval stopping, activation is consistently lower during No-Think than Think trials in left and right hippocampi. Such negative BOLD responses (NBRs) do not arise when people instead avoid recalling the target by retrieving distracting thoughts[24], underscoring that hippocampal reductions during No-Think trials are specific to retrieval cancellation. NBRs arise when people suppress neutral words[15,24,65–70,125–127], negative words[69,126], neutral scenes[33,48,72], negative scenes[71,73,74], neutral visual objects[51,56], and neutral and negative autobiographical memories[46]; and they appear robustly in quantitative meta-analyses[113]. The generality of hippocampal BOLD reductions across stimuli, regardless of valence suggests that hippocampal modulation contributes to regulating diverse content. Reduced hippocampal activation occurs as part of a broader NBR pattern during No-Think trials, which includes bilateral posterior perirhinal area 36, entorhinal and parahippocampal cortices[15], retrosplenial cortex (BA 29/30), posterior cingulate cortex (BA 23), bilateral lingual gyrus, cuneus, and right ventromedial prefrontal cortex (BA 25, subgenual ACC). This wider pattern indicates that retrieval stopping broadly interrupts default mode network activity[128], perhaps by truncating hippocampal outputs that drive cortical reinstatement during retrieval, or by targeting cortex itself (see later section on Parallel Modulation of Hippocampus and Cortex).

NBRs don't necessarily indicate that suppression downregulates hippocampal activity. Indeed, whether NBRs reflect actively suppressed activity has been widely discussed, with evidence for and against[129–135]. Moreover, lower No-Think trial activity might simply reflect higher hippocampal engagement during Think trials. However, wider evidence suggests that the hippocampal NBR reflects inhibitory control's impact. First, suppression reduces hippocampal activity below a fixation baseline[24,48,67,71], sug-

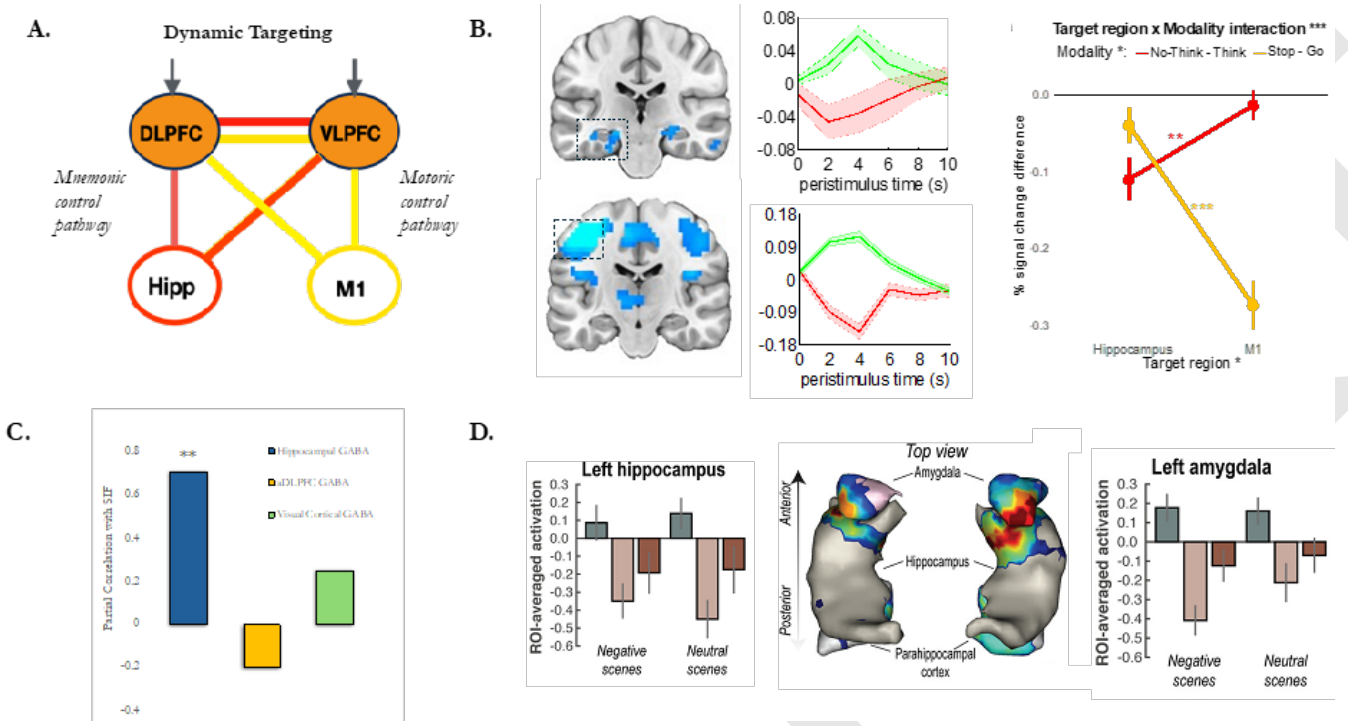


Figure 4. Stopping intruding thoughts engages a distinct fronto-temporal mnemonic control pathway. **a**, Dynamic targeting of inhibitory control; Effective connectivity (dynamic causal modelling) analyses reveal that the same right aDLPFC and VLPFC regions shift from modulating motor area M1 (yellow) to modulating the hippocampus (red) after transitioning from action to thought stopping blocks, implying distinct motoric and mnemonic control pathways. Arrows indicate driving inputs to the network. **b**, In the study from panel a, control reduced BOLD signal in bilateral hippocampus (top) or left motor area M1 (bottom) during retrieval and action stopping respectively. BOLD time courses in left hippocampus and left M1 shows increased activity during Think and Go trials, and reduced activity during No-Think and Stop trials. Illustrating targeted modulation, a double dissociation arose such that stopping thoughts modulated hippocampus more than M1 (red line, right panel in b), whereas stopping actions modulated M1 more than hippocampus (yellow line, right panel in b) (** = $p < .01$; *** = $p < .001$). **c**, Hippocampal modulation reflects prefrontal-influences on GABAergic interneurons local to the hippocampus; Higher hippocampal, but not prefrontal or visual cortical GABA predicts superior SIF (and greater hippocampal modulation; not depicted). **d**, Retrieval stopping countermands intrusive thoughts, with effects extending beyond the hippocampus; Suppressing scenes down-regulates activity more on trials when intruding thoughts are reported (light tan bar) than on non-intrusion trials (brown bar) (Think trials in grey). Suppressing negative scenes reduces activity in both the hippocampus and amygdala (left and right graphs, panel d). Greater down-regulation of common voxels in the anterior hippocampus and amygdala (during intrusions compared to non-intrusions) predicted better intrusion control (reduced intrusion frequency) and greater reductions in negative valence. Colours reflect scores from a latent factor derived from partial least-squares analysis.

gesting that lack of retrieval isn't the sole explanation. Second, right aDLPFC activation during No-Think trials often negatively correlates with hippocampal activity[71,72]. That reduced hippocampal activity accompanies prefrontal engagement suggests that aDLPFC contributes to reductions. Effective and functional connectivity findings reinforce this impression. For example, Dynamic Causal Modelling reveals a causal influence of right aDLPFC on hippocampal activity during suppression[24,33,48,51,56,67,68] and an influence of rVLPFC[68] (Fig. 4b). Connectivity between the prefrontal cortex and the hippocampus is typically negative and coupling strength predicts forgetting[24], and intrusion declines over suppression trials[48]. Using psychophysiological interaction analysis (PPI), seeding the hippocampus, Schmitz et al.[67] found that aDLPFC's connectivity with the hippocampus differed during Think and No-Think trials, exhibiting negative coupling in the latter. Hippocampal modulation by right aDLPFC also has been found with Granger Causality on source-resolved EEG data,[66] mitigating concerns about the interpretation of hemodynamic measures.

Compelling evidence for hippocampal modulation has been reported with the item-method directed forgetting procedure using effective connectivity analysis on intracranial EEG data. Oehrn et al.[105] studied 25 patients with intracranial electrodes in the DLPFC, the hippocampus, or both (n = 6 in the last case). Recording activity elicited by the Remember and Forget instructions revealed distinct processes engaged during forgetting that altered information flow from the DLPFC to the hippocampus. Attempting to forget triggered greater EEG activity in low-theta (3–5 Hz) in the DLPFC, emerging 568–1058 ms after the Forget cue. Critically, effective connectivity analyses revealed DLPFC interactions with the hippocampus in the low beta range (15– 18 Hz), echoing prefrontal beta power changes during both retrieval stopping and action stopping[97]. Top-down beta-mediated interactions dominated only during Forget trials beginning in the DLPFC 100–130 ms prior to affecting the hippocampus. These data provide spatially and temporally specific support for a top-down signal of encoding suppression via inhibitory control. In healthy humans, successful directed forgetting reduces hippocampal

activity, and right DLPFC negatively couples with the left hippocampus[136]. Together, these findings establish diverse evidence for DLPFC's causal role in reducing hippocampal activity, consistent with the proposed fronto-temporal inhibitory control pathway.

Suppressing a thought by retrieval stopping also reduces electrophysiological markers of hippocampal retrieval. One such marker is theta-band activity. Abundant animal and human work shows that retrieval depends on hippocampal–cortical synchronization supported by the theta rhythm[137–139]. In humans, non-invasive studies indicate that retrieval increases oscillatory power[140,141] and long-range phase synchronization in the theta band[142,143]. Moreover, intracranial EEG recordings in the human hippocampus[144] show that low frequency theta power increases and phase reset are associated with successful memory retrieval[145]. Crucially, directing attention to one's thoughts increases theta-band connectivity between the default-mode network (including the hippocampus) and fronto-parietal control networks[146]. Given these considerations, intentionally suppressing thoughts via retrieval stopping should reduce hippocampal theta power. Confirming this, theta power reductions during No-Think trials often emerge 500 ms after cue onset and extend throughout the several-second trial[54,147,148]. Suppression-induced theta reductions have been source localized to the medial-temporal lobes[148] and posterior visual cortex and are often greater for participants who successfully forget. Importantly, a simultaneous fMRI/EEG study associated the hippocampal NBR during retrieval stopping with suppressed hippocampal theta oscillations[66]. Moreover, on a trial-wise basis, hippocampal theta power positively coupled with right hippocampal BOLD signal and was reduced on trials with higher BOLD activation in right aDLPFC. These findings support the view that hippocampal NBRs during retrieval stopping reflect the fronto-temporal inhibitory control pathway's impact.

Reactive Control and Hippocampal Suppression

Inhibitory control's impact on the hippocampus appears to be driven reactively when unwelcome thoughts intrude. Levy and Anderson[15] illustrated this link. Participants classified their experience after each trial according to whether the cue triggered its associated memory (intrusions) or not (non-intrusions) (Fig. 2b). No-Think trials accompanied by intrusions elicited bilateral hippocampal down-regulation. Although modest down-regulation occurred on non-intrusion trials, intrusions triggered deeper reductions because mnemonic awareness needed to be terminated. Strikingly, during intrusions, down-regulation's depth predicted later SIF (r = .66) but did not during non-intrusions (r = -.04). Intrusion-related down-regulations also extended more broadly, including anterior and posterior hippocampus, entorhinal, perirhinal, and parahippocampal cortices. Greater hippocampal down-regulation during intrusions arises when people suppress neutral words[15], neutral visual objects[51], neutral scenes[33,48] and aversive scenes[33] (Fig. 4d).

Reduced hippocampal activation during intrusions violates expectations for how hippocampal activation should relate to retrieval. Episodic retrieval increases hippocampal BOLD signal across diverse materials[124,149–151], presumably reflecting neural activity driving pattern completion processes that enable recollection. Hippocampal activation during intrusions inverts this pattern: intrusions, on which retrieval occurred, show less activation than non-intrusions, on which no retrieval occurred. Notably, intrusions and non-intrusions show less activation than do Think trials; thus, voluntary retrieval increases BOLD signal, verifying the ability to measure recollection-related activity. Together, these findings suggest that some additional factor operates during intrusions that counteracts retrieval-related hippocampal activation. Levy and Anderson[15] posited that intrusions trigger top-down control by the right DLPFC that suppresses hippocampal activity, countermanding recollection. Thus, hippocampal modulation constitutes a *reactive control response* that cancels an emerging retrieval. In contrast, non-intrusion trials may reflect retrieval *prevention* by *proactive control*, acting prior to hippocampal pattern completion. This account explains the selective relationship between SIF and intrusion-related down-regulation, if hippocampal down-regulation disrupts recently reactivated hippocampal traces. Consistent with reactive control during retrieval stopping, effective connectivity analyses have found that right MFG's top-down coupling with the hippocampus is negative, and stronger during intrusions than non-intrusions[33,51].

The foregoing patterns could indicate inhibitory control's selective engagement by intrusions. Alternatively, during non-intrusions, inhibitory control may affect regions outside the hippocampus. Indeed, inhibitory control could theoretically interrupt any point in the mechanistic cascade supporting retrieval, including cue processing, transmitting cue input into the hippocampus, pattern completion, hippocampal output, pattern reinstatement in neocortex, the entrance of reinstated content into working memory, or the expulsion of that content[71]. Confirming such early or late retrieval effects requires greater temporal resolution than fMRI provides.

EEG studies, however, offer a temporally precise window into retrieval stopping that has proven useful in isolating intrusion control. For example, one approach assumes that intruding thoughts enter working memory after cortical reinstatement of the retrieved content in response to hippocampal pattern completion. If so, No-Think trials with intrusions may exhibit increased ERP indices of working memory storage. Inhibitory control may then rapidly purge working memory, and such dynamics may be detectable with working memory markers. Hellerstedt et al.[50] tested this possibility using the frontal negative slow wave (NSW) working memory index[152]. They found that whereas during Think trials, the NSW emerged within 550 ms and lasted the whole trial, No-Think trials without an intrusion showed no NSW. Critically, intrusions triggered an NSW that persisted for 1500 ms, but which was rapidly eliminated, with the NSW's duration inversely

related to SIF. These findings track intruding content's emergence into and then purging from working memory. Quantifying intrusion duration in working memory revealed that rapid purging is key to forgetting. Retrieval stopping also modulates ERP markers of episodic recollection, such as the parietal episodic memory (EM) effect: this parietal response increases during Think trials, but not during suppression[25,153]. Suppression also abolishes memory reinstatement detected by item-specific EEG decoding of unwanted content, starting as early as 3-600 ms after reminder onset[154]. Together, these findings indicate that reactive control's impact emerges as early as the likely onset of episodic recollection (500 ms post-cue[138]), consistent with a rapid, reactive deployment of inhibitory control.

Although the foregoing findings suggest that intrusive thoughts trigger hippocampal modulation, they do not specify what initiates the control signal. Some mechanism must detect intrusions and signal right aDLPFC to modulate hippocampal activity. The dACC may serve this role. In non-memory contexts, major theoretical accounts posit that dACC monitors processing and detects information indicating a need to intensify control, and then communicates this demand to prefrontal control regions[155–159]. Thus, dACC may monitor for and signal intrusive thoughts' occurrence, upregulating inhibitory control. Specifically, when proactive control fails to prevent retrieval, dACC signals triggered by the hippocampus may initiate a reactive mechanism, engaging rDLPFCi to suppress hippocampal retrieval[15,33,48].

Crespo-García et al.[66] tested these hypotheses with simultaneous fMRI and EEG. They exploited EEG's superior temporal resolution to track inhibitory control dynamics and relate EEG indices of these dynamics to BOLD signals. The study focused on mid-frontal theta power and the N2, two electrophysiological measures linked to cognitive conflict. In non-memory tasks, increased midline and prefrontal theta activity typically reflects enhanced cognitive control, and is a common mechanism by which ACC and mPFC detect the need for control and communicate that need to lateral PFC[159]. Retrieval stopping increases mid-frontal theta[148,160] and N2 effects[25,47,98,99,161]. Based on these findings, Crespo-García hypothesized that if a thought intrudes, mid-frontal theta as well as dACC activation should increase. During retrieval stopping, Crespo-García indeed observed both source-localised theta and BOLD signal increases in dACC and a positive correlation between these indices. Importantly, on a trial-wise basis, high dACC conflict during No-Think trials was associated with (a) increased effective connectivity between the dACC and right aDLPFC, (b) increased effective connectivity between the right aDLPFC and the hippocampus in the 1 second following conflict, and (c) reduced source-resolved hippocampal theta, a marker of hippocampal retrieval. Strikingly, hippocampal theta power was elevated during high-conflict compared to low conflict trials during the first 1600 ms of No-Think trials, consistent with a short-lived intrusive retrieval; this effect disappeared for the trial's remainder, as predicted by a reactive process that suppresses retrieval. Theta reductions in the later time window were linked to hippocampal BOLD reductions, as well as increased dACC and right aDLPFC BOLD signals. These findings constitute temporally and spatially specific evidence linking the early detection of unwanted hippocampal retrieval by the dACC, the signalling of conflict to the right aDLPFC, and aDLPFC's upregulation to suppress hippocampal retrieval. Importantly, hippocampal suppression induces forgetting that reduces future intrusion-related ACC/DLPFC reactive control activity, yielding what is known as an adaptive *conflict reduction benefit*[32,48,162].

The foregoing findings highlight how successfully purging intrusive thoughts may not solely rely on prefrontal function, but also the hippocampus, and the broader fronto-temporal pathway. Findings by Mary et al.[51] illustrate this point and its immediate relevance to post-traumatic stress disorder. They studied retrieval stopping in 102 survivors of the Paris Terrorist attacks on November 13, 2015. Most participants were terror targets, and many developed PTSD. Mary compared retrieval stopping in survivors who developed full or partial PTSD (PTSD group, n = 55), those who did not (Traumatized Controls, n = 47) and non-traumatized citizens (Control, n = 73). Participants were scanned during a TNT procedure involving neutral word-object associations (e.g., object photos, like a football). Mary tested suppression's impact on retention with a perceptual identification task for the objects[56,57]. Participants with PTSD showed impaired SIF on this implicit perceptual measure, extending similar deficits found with explicit memory[163]. This suggests that weak memory control is a risk factor in developing PTSD.

Using dynamic causal modelling, Mary et al.[51] found that for traumatised controls, right DLPFC modulated hippocampal activity and modulatory parameters were more negative during intrusions than non-intrusions, replicating prior work[33]. Importantly, the PTSD group showed deficient fronto-hippocampal modulation during intrusions, a characteristic that may underlie traumatic intrusions. Later analyses revealed a contributor to deficient control. Using a high-resolution structural scan, Postel et al.[164] discovered that participants who developed PTSD had reduced volume in hippocampal subfield CA1 compared to both control groups. Models of hippocampal function hypothesize that subfield CA1 receives pattern completion outputs from CA3, facilitating communication needed for cortical reinstatement[165]. Strikingly for participants with PTSD, lower CA1 volumes predicted greater traumatic re-experiencing; in resilient individuals, greater CA1 volumes predicted more negative prefrontal-hippocampal effective connectivity during intrusions in the TNT task. These findings suggest that inhibitory modulation of hippocampal activity may suppress pattern completion inputs to CA1. Thus, a compromised CA1 may dysregulate control. Broadly, these findings illustrate how inhibitory control over thought relies on unique features of the fronto-temporal inhibitory control pathway[166].

Systemic Hippocampal Suppression

How targeted is thought suppression's impact on hippocampal activity? Reduced hippocampal activation might reflect selective inhibition of the suppressed thought; alternatively, suppression might globally suppress hippocampal activation, triggered by an intruding thought[19,28,167]. Such a "global stopping" mechanism exists for action inhibition. For example, in the Stop-Signal task, terminating an action broadly modulates motor cortical excitability, even for effectors uninvolved in the action[168–170]. Thus, stopping specific actions, arises via broad motor cortical inhibition. A parallel mechanism of generalized inhibition could underlie intrusion-related hippocampal suppression. If inhibitory control globally suppresses the hippocampus, it may impede all hippocampal processes, including encoding, consolidation, and retrieval, a possibility referred to as *mnemonic process inhibition*[171]. If so, suppressing hippocampal activity may induce a "virtual lesion", mimicking organic amnesia[125,172,173].

Several studies address predictions of this global suppression mechanism. Global suppression would induce an *amnesic shadow* for memories encoded near in time to the retrieval stopping event, even when unrelated to suppressed content. Thus, just as hippocampal damage induces retrograde and anterograde amnesia, so too should transient hippocampal dysfunction due to suppression. To test this prediction, Hulbert et al.[125] inserted pictures between Think and No-Think trials and tested them after the TNT task. These "innocent bystander" pictures featured an object in a background, and participants imagined how the object got there. If thinking about the picture encodes a hippocampal trace, and if suppression follows, will bystander memory suffer? If retrieval stopping happens before the bystander, will hippocampal down-regulation induce an adverse hippocampal state, disrupting bystander encoding?

Hulbert et al.[125] found that pictures surrounded by No-Think trials exhibited sizeable recall deficits compared to those surrounded by Think trials. Bystander pictures suffered as high as a 44% proportional retention loss. Importantly, this amnesic shadow only occurred when people canceled retrieval and not when they avoided No-Think targets by retrieving distracting thoughts. Hulbert further showed that this amnesic shadow (a) arose from retrieval stopping, not task difficulty, (b) reflected bystander memory disruption by No-Think trials rather than enhancement by Think trials, (c) included anterograde and retrograde amnesia effects, and (d) lasted at least 24 hours. Interestingly, the amnesic shadow also affected bystander recognition, with a caveat: it spared old/new recognition, but impaired source memory. The amnesic shadow's specificity to source memory points to hippocampal disruption, given the hippocampus's greater role in recollection than familiarity[174–176]. These memory deficits correlated with hippocampal down-regulation during retrieval stopping[125]. The amnesic shadow thus suggests that retrieval stopping does more than merely terminate retrieval mode[31], inducing a state akin to a hippocampal lesion, disrupting encoding and consolidation. These findings imply that inhibitory control suppresses unwanted thoughts not by inhibiting individual memories, but by globally suppressing hippocampal activity.

The amnesic shadow also affects older memories reactivated near retrieval stopping[177,178]. Zhu et al.[177] had participants encode bystander memories before TNT training. Bystanders were scenes, each associated to two cues: an object and a word. During the TNT phase, instead of bystander encoding between Think and No-Think trials, a bystander's object cue appeared, and participants decided whether they recognized it. Importantly, half the cues appeared subliminally, masked by white noise. Prior work suggests that even imperceptible cues subliminally activate associated memories in the hippocampus[179–184], potentially rendering them vulnerable. Indeed, participants showed an amnesic shadow for bystanders cued between No-Think trials, compared to those cued between Think trials, and also to Baseline pairs learned initially, but not cued during the TNT phase. The shadow arose even for subliminally reactivated scenes, and even when tested with the second (word) cues that never appeared during the TNT phase. These findings illustrate that bystander forgetting induced by hippocampal suppression was cue independent. In contrast, scenes cued between Think trials showed no effects.

Systemic hippocampal suppression holds broader lessons about inhibitory control. Historically, two views of how control suppresses interference have been discussed: *direct inhibition* and *biased competition*[19,28]. Direct inhibition posits that control processes inhibit representations (directly or by exciting inhibitory interneurons). Biased competition, however, hypothesizes that attentional control facilitates desired representations, and that local reciprocal inhibition inhibits competitors. Biased competition's role in suppressing interference is established[28,185,186]. However, both types of control occur. Using high-resolution methods from the system to the synapse, studies in rhesus monkeys show that the prefrontal cortex can exercise inhibitory control when its excitatory pathways leave the cortex, travel via white matter and innervate inhibitory neurons at the termination site[187–189]. Systemic suppression implied by the amnesic shadow reflect this direct inhibition[125]. Thus, systemic suppression may be a key memory control mechanism reflecting a broad principle of inhibitory control.

Hippocampal GABAergic Inhibition

How does the prefrontal cortex suppress hippocampal function? The pathways linking cortices with each other or with subcortical structures are overwhelmingly excitatory in primates[166,190], making it unlikely that prefrontal projections are inhibitory. One possibility is that prefrontal projections, via polysynaptic pathways, drive hippocampal interneurons, interrupting oscillatory functioning and suppressing hippocampal activity (BOX1). By this hypothesis, retrieval stopping's outcomes, including intrusion-

related hippocampal down-regulation, reduced hippocampal theta power, SIF, and the amnesic shadow, reflect disruptions driven by input to inhibitory neurons.

Multimodal imaging can be used to test whether hippocampal interneurons contribute to retrieval stopping[67]. If prefrontal input during thought suppression engages hippocampal inhibitory interneurons, BOLD reductions may correlate with hippocampal gamma aminobutyric acid (GABA), because hippocampal interneurons are GABAergic. Schmitz et al.[67] quantified hippocampal, prefrontal, and visual cortical GABA with magnetic resonance spectroscopy, and conducted fMRI during the TNT task, providing co-localized BOLD signal and GABA measures. Strikingly, higher resting hippocampal GABA predicted greater hippocampal down-regulation during retrieval stopping and more successful forgetting of the thoughts people suppressed (Fig. 4c). Resting prefrontal or visual cortical GABA, however, predicted neither hippocampal BOLD signal, nor forgetting, confirming hippocampal GABA's unique importance. Effective connectivity analyses established that the right aDLPFC modulated the hippocampus for higher, but not lower hippocampal GABA participants. Thus, hippocampal GABAergic interneurons may enable prefrontal inhibitory control signals to suppress hippocampal retrieval, disrupting unwanted thoughts, consistent with a fronto-temporal inhibitory control pathway.

Schmitz et al.[67] demonstrates a factor influencing thought suppression success with no relationship to action inhibition: hippocampal GABA. Indeed, no action inhibition account includes control pathways modulating hippocampal activity, which has little relevance to regulating action. If hippocampal GABAergic tone determines the success of top-down control over thoughts and forgetting rate, this feature illustrates why measuring action inhibition constitutes a poor proxy for thought stopping capacity. Indeed, Schmitz's design establishes this point directly. During the TNT phase, action and retrieval stopping blocks were interleaved. On action stopping blocks, hippocampal activation during Stop trials was unrelated to hippocampal GABA and later SIF, revealing that action stopping does not suppress hippocampal activity. Indeed, action stopping yielded no evidence for prefrontal-hippocampal connectivity. Hippocampal GABA also did not predict Stop-Signal reaction time. Together, these findings indicate that hippocampal GABA uniquely impacts thought stopping success.

BOX 1: Hippocampal GABA's Role in Intrusive Thinking.

The DLPFC initiates a top-down control signal to cancel retrieval, but this signal's capacity to suppress hippocampal retrieval depends on hippocampal GABA[67]. Hippocampal GABAergic interneurons serve diverse and complex functions, including roles in driving/shaping endogenous gamma and theta oscillations, sharp-wave ripples, and place fields used during spatial navigation, and modulating synaptic plasticity[191–193]. We suggest here that the endogenous regulation of GABAergic interneuron networks in the hippocampus by the prefrontal cortex also plays a critical role in cancelling retrieval, and that the capacity to achieve this may be related to global measures of hippocampal GABA in humans. If so, the capacity to drive hippocampal GABAergic inhibition constitutes a unique parameter downstream to the prefrontal cortex that governs thought stopping success—a parameter independent of prefrontal function. This parameter's influence during thought suppression may organize clinical and preclinical research on psychiatric disorders.

Research on psychiatric disorders has converged independently on the association between intrusive thoughts and hippocampal GABA. Patients with psychiatric disorders featuring intrusive thoughts, often exhibit elevated resting hippocampal activity[194–200], a pattern termed "hippocampal hyperactivity" or "hippocampal disinhibition." In schizophrenia, the severity of positive symptoms, such as hallucination, increases with hippocampal hyperactivity, as indexed by abnormally elevated resting blood-oxygen-level dependent (BOLD) activity, or increased regional-cerebral blood-flow, blood-volume, or blood-glucose metabolic rate[194,197]. Hyperactivity gives rise to and is exacerbated by dysfunctional GABAergic interneurons[201], and post-mortem anatomical studies confirm substantial hippocampal parvalbumin-positive and somatostatin-positive interneuron loss[194,198,202]. Animal models of schizophrenia that disrupt hippocampal GABAergic inhibition by transgenic or pharmacological manipulations reproduce hippocampal hyperactivity and volume loss, along with behavior paralleling symptoms of this disorder[201,203,204]. Elevated hippocampal activity also occurs in PTSD and major depression, and this pattern predicts flashback intensity and depressive rumination[195,196,199,200,205]. Here too, impaired hippocampal GABAergic inhibition could contribute, possibly induced by stress[192,206–208]. Strikingly, animal models of anxiety often focus on compromised hippocampal GABAergic interneurons, which produce symptoms reflecting dysregulated affective control[209,210], including impaired fear extinction[211]. Indeed, human hippocampal GABAergic interneurons are reduced in postmortem studies of anxiety[192]. These findings suggest that deficient hippocampal GABAergic inhibition is broadly associated with intrusive memories and thoughts. Indeed, a large-scale (n = 427,037) genome-wide association study strongly associated general executive function (which may be related to inhibitory control[107]) with psychopathology and with genes related to GABAergic function[212].

Diminished hippocampal GABA may also contribute to difficulty *suppressing default network activity* arising across psychiatric disorders with intrusive symptomatology[200]. If diminished hippocampal GABA makes it hard for the right aDLPFC to suppress intrusive thoughts, automatic retrieval activity should prevail, activating the broader default network[213–215]. Such activity may occur even during

controlled task states. Consistent with this possibility, a large-scale (N = 663) analysis relating psychiatric symptoms to resting state data revealed deficient network segregation between the default mode and the fronto-parietal control network that co-occurred trans-diagnostically with a range of symptoms[216]. Reduced network segregation may be a network-level consequence of a compromised fronto-temporal inhibitory control pathway originating from hippocampal GABAergic deficits: less GABA may yield hippocampal disinhibition and persistent intrusive thoughts, amplifying a tendency to focus attention inwardly, rather than to the external world[217] and integrating fronto-parietal and default network activity[146].

Parallel Suppression of the Hippocampus and Cortex

Retrieval stopping also affects neocortical areas, a discovery that emerged in early fMRI studies, being apparent in visual cortex[65,71]. Gagnepain et al.[56] showed that suppression also targets higher cortical regions representing thought content. Gagnepain asked participants to suppress visual objects associated to word cues. Using objects allowed Gagnepain to identify object-related regions that inhibitory control might target. With an object perception localizer task, Gagnepain identified fusiform cortex and lateral occipital complex (LOC); because the former had been associated with conscious object perception[218,219], it was a candidate target region to suppress conscious object intrusions. Suppression reduced activation during No-Think compared to Think trials in this fusiform ROI. Effective connectivity analyses revealed that right MFG modulated hippocampus, fusiform, and the LOC in parallel during retrieval stopping.

Gagnepain et al. also scanned participants during the test after the TNT task, to measure persisting neural aftereffects on suppressed traces. They tested retention with perceptual identification (a perceptually-oriented implicit memory task) in which participants identified objects in visual noise. In such tasks, people identify studied objects faster than novel objects, a form of perceptual priming[220]. There was priming for all studied objects, compared to novel objects. Previous viewing of an object reduces the BOLD response on later presentations, compared to responses to novel objects; this reduced response, known as neural repetition suppression, is taken to reflect perceptual memory's impact on cortical processing[220,221]. Replicating this pattern, Gagnepain found repetition suppression for all studied objects. Critically, however, stopping object retrieval during No-Think trials reduced later repetition suppression in fusiform cortex and LOC, compared to repetition suppression for Baseline or Think items. Retrieval stopping had disrupted the neural signature of perceptual memory, revealing a neural aftereffect of inhibitory control. Indeed, prefrontal-fusiform inhibitory coupling during No-Think trials, predicted disrupted repetition suppression on the final test.

Neocortical down-regulations such as those observed by Gagnepain et al. may be triggered by intruding thoughts. Upon seeing a reminder, if inhibitory control does not quickly suppress hippocampal pattern completion, the hippocampus may rapidly reactivate neocortical regions via re-entrant pathways. Indeed, the hippocampus drives neocortical activity related to an initial experience during intentional retrieval, and implicit memory[1–4,222,223], with involuntary retrieval supported by a similar rapid process[224–227]. This rapid cortical reinstatement, experienced as an intrusion, may up-regulate and retarget inhibitory control in parallel to the hippocampus and the cortical region. Thus, during intrusive thoughts, rapid reactivation and then reactive suppression of content-related cortical regions should occur[56]; if thoughts concern an object, a scene, or aversive content, control might target the fusiform cortex, the parahippocampal place area, or the amygdala, respectively. The content the hippocampus reinstates should dictate the regions targeted, which we refer to as *the reinstatement principle*[33].

Work on visual scene suppression also supports the reinstatement principle. Suppressing unpleasant scenes reduces parahippocampal place area and amygdala activation, more so during intrusions than non-intrusions[33]. Because encoding unpleasant scenes likely recruits the parahippocampus and amygdala, and because these regions receive output projections from the hippocampus[228–231], hippocampal pattern completion is predicted to reinstate activation in both, triggering an intrusion and a reactive control response. Indeed, dynamic causal modelling revealed that right aDLPFC modulated the hippocampus, parahippocampus and the amygdala in parallel, with intrusions yielding more negative top-down coupling. Deeper intrusion-related down-regulations in the anterior hippocampus and the amygdala predicted reduced intrusion frequency and negative valence perceived in the scenes after the task. These findings support the reinstatement principle and link the fronto-temporal inhibitory control pathway to the disruption of affective memory.

Suppressing reinstated scene memories not only down-regulates the parahippocampus, but also disrupts retention. For example, after encoding object-scene associations, Meyer and Benoit[74] had participants perform three tasks during fMRI scanning. First, they covertly recalled each scene (given its cue) and rated its vividness. A TNT task followed, with participants suppressing or retrieving the scenes. Finally, they again retrieved the scenes and rated their vividness. Replicating past work, suppressing scene imagery engaged right aDLPFC and reduced bilateral hippocampal and parahippocampal cortex activity[33,48]; it also rendered suppressed content less detailed and vivid[42,74,154,163,232]. A classifier trained to distinguish scenes from morphed scenes revealed that, during retrieval stopping, suppression reduced scene information in the parahippocampal cortex. Critically, this effect persisted into the final test: relative to retrieval before the TNT task, No-Think scene information was reduced, and more than for Baseline items. With representational similarity anal-

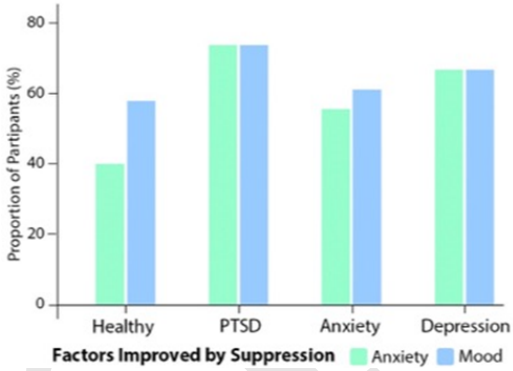
ysis, Meyer further showed that reduced scene-specific parahippocampal pattern information predicted diminished vividness. These findings underscore cortical modulation's importance during thought suppression, showing that modulation adapts both thought accessibility and precision[42,233]. Reduced hippocampal-visual cortical (lingual gyrus, cuneus) connectivity during retrieval stopping predicts SIF on explicit tests, suggesting that suppression disrupts connectivity in addition to cortical representations[234].

Thought suppression's tendency to inhibit neocortical activity extends its impact to implicit memory. For example, suppressing visual objects impairs perceptual repetition priming, reducing cortical representations' perceptual influence[51,56,57]. Similar effects arise in conceptual implicit memory. Wang et al.[60] found that suppressed concepts arose less often as solutions on Remote Associates Test creativity problems than did baseline concepts. Impaired conceptual implicit memory suggests that suppression affects temporal or perirhinal cortices along with the hippocampus. Similarly, participants verify suppressed items' category memberships more slowly than those of baseline items[59], and suppressed items emerge less often on free-association measures[58]. Effects on subjective valence and physiological emotion measures extend suppression's impact beyond explicit memory[49,54,232,235,236](Box 2). Thus, retrieval stopping modulates diverse content on direct and indirect tests, constituting a broad model of inhibitory control over thought.

BOX 2: Affective Consequences of Thought Suppression.

People often suppress thoughts to reduce the worry, fear, guilt, anger, shame, or sadness that they trigger. This behavior suggests that retrieval stopping regulates emotions and reduces distress[41,237–240]. Retrieval suppression modulates immediate and longer-term affect. During suppression, immediate subjective negative affect[241], and amygdala activation[33,71,73,96,235] are reduced especially when the content intrudes and must be purged[33]. After suppression, affective responses to suppressed content show persisting attenuation. On subjective measures, successfully suppressing aversive scenes reduces valence[33,49,54,236] and anxiety ratings for feared events[232,235]. On psychophysiological measures, suppressing aversive scenes reduces skin conductance responses upon re-exposure to suppressed scenes[49,73], as well as heart rate deceleration[54]. Similarly, directing people to forget pictures associated with electric shock (via Pavlovian conditioning) reduces memory for the pictures and skin conductance response to them[242]. Affective changes have been associated with suppression's parallel impact on the anterior hippocampus and the amygdala (Fig. 4d), especially during intrusive thoughts[33].

The foregoing findings show that engaging inhibitory control to suppress upsetting thoughts impairs memory and regulates emotion for laboratory materials. These benefits extend to suppressing real-life fears of individual participants[235]. For example, training people to suppress distressing thoughts about feared future events yields significant mental health benefits on immediate and delayed assessments, especially for participants with higher anxiety, depression, or PTSD[232] (Figure).



These findings strongly challenge clinical wisdom that suppressing thoughts is maladaptive. They are consistent, however, with the possibility that suppressing aversive thoughts engages affective stopping mechanisms that regulate emotion (Fig. 3). For example, in the retrieval stopping model of fear extinction[114], repeated unreinforced presentations of a conditioned stimulus signal that the feared outcome will no longer occur, triggering thought suppression to diminish fearful thoughts and attenuate affect. Consistent with this proposal, a conjunctive meta-analysis of fear extinction and retrieval stopping studies reveals robust shared right aDLPFC engagement and reduced hippocampal activity (Rowlands et al.[113]). Inhibitory control over thought may be essential to affect regulation and mental health[41].

Intrusive Thoughts as Mnemonic Capture

How might cortical reinstatement trigger parallel, reactive control over the hippocampus and cortex? One possibility is that intrusions capture attention, triggering control[168]. Intrusive thoughts arise involuntarily[243] and, as in the TNT task, they can occur despite suppression effort. They are not merely unintentional, but counter-intentional[52]. These features suggest intrusive thoughts are instances of *attentional capture*[244–247], specifically mnemonic capture[168,248,249]. Direct evidence comes, for example, from EEG classifiers, where training based on visual attentional capture enables cross-task classification of scene memory intrusions during retrieval stopping[53]. The timing of attentional orienting to the scene corresponded well with conscious recollection's speed in general[138], and with intrusion timing during retrieval stopping[50,66]. Consistent with attentional orienting, intrusions during No-Think trials engage ventral attention regions such as the right supramarginal gyrus, that co-localize with visual capture activations. Within the right supramarginal gyrus and

temporo-parietal junction, the intrusion/non-intrusion distinction can be decoded using a classifier trained to distinguish invalid and valid cuing in the spatial orienting task[250]. These findings suggest that memory and perception engage common attentional orienting and selection mechanisms[217,251,252].

The ventral attention system's influence on the ACC may trigger reactive control of intruding thoughts via the right aDLPFC and this orienting process may span inhibitory control domains[11,168]. ACC may be driven in part by the anterior Insula (Fig. 3b), to facilitate right aDLPFC's recruitment, consistent with the Insula's role in detecting salient events[253] and switching between default and executive networks[254–256]. More broadly, these findings underscore interactions of our fronto-temporal inhibitory control pathway with attention and salience networks during thought suppression[257]. Indeed, resting state connectivity of the fronto-parietal control network, and its interactions with attentional networks[258] robustly predicts forgetting intrusive thoughts. Intriguingly identifying attention's role also reveals that stopping intrusive thoughts could arise by *suppressing ventral attention system orienting* rather than the thought's representation[259–261]. Thus, inhibitory control may sometimes implement a *drift resistance policy* to facilitate concentration and reduce mind-wandering by attentional capture.

Pathways Mediating Fronto-Temporal Inhibitory Control

Several hypotheses exist about the pathways mediating right aDLPFC's and VLPFC's suppression of hippocampal and neocortical activity. Studying these pathways will illuminate which features thought and action stopping share, and which are unique.

Dual Pathway Account. Rodent and primate anatomical studies historically have found no long-range projections allowing the prefrontal cortex to directly impact hippocampal function, especially long-range inhibitory projections[166] (however, see[262]). Most accounts posit polysynaptic pathways underlying hippocampal modulation. Anderson, et al.[166] proposed a dual pathway model focused on the dACC that explains proactive and reactive thought stopping. Retrieval stopping engages the dACC and meta-analyses indicate co-localized activations across action and thought stopping (Fig. 3b)[68,93] that predict SSRT and SIF[68]. Although the dACC supports conflict detection[66], BA32 may also mediate right aDLPFC's influence over MTL. The dACC has strong and diverse connections with the rest of PFC, including area 9/46 in DLPFC[263]. Thus, engaging area 9/46 could influence dACC. Moreover, dACC strongly links with MTL, the amygdala, and the hypothalamus[263–266]. These characteristics position dACC to receive top-down excitatory inputs from aDLPFC and propagate that influence to control memory and emotion areas.

ACC does not project directly to the hippocampus[267–270]. Nevertheless, ACC projections could affect hippocampal retrieval proactively or reactively (Fig. 5a). First, the ACC may suppress cortical inputs into the hippocampus, a possibility that Anderson et al. (2015) refer to as the *entorhinal gating hypothesis* (Fig. 5a). In primates, ACC preferentially projects to medial rhinal areas (28 and 35) and parahippocampal cortices (TH/TF). In MTL, ACC pathways terminate in the upper and deep layers, where they target excitatory and inhibitory postsynaptic targets citepApergisSchoute2006Ultrastructural. In the ACC area 32 pathway, synapses with inhibitory neurons preferentially affect powerful parvalbumin (PV) neurons in the rhinal cortices' deep layers[271]. By engaging PV interneurons, ACC can suppress excitatory inputs from temporal cortex that would otherwise propagate to the hippocampus, driving retrieval (also outputs leaving the hippocampus). Gating cue input may induce hippocampal and perirhinal quiescence during retrieval stopping (see also[167]). Relatedly, intracranial recording studies in epileptic patients have proposed that frontal cortices influence hippocampal encoding by affecting rhinal cortices[272]. Notably, however, entorhinal gating would prevent pattern completion, not suppress it. If pattern completion increases BOLD signal, entorhinal gating would yield lower hippocampal activation in the No-Think than in the Think condition, even though hippocampal processing would not be actively suppressed. Thus, entorhinal gating may not explain memory disruption or hippocampal down-regulation. Entorhinal gating could be deployed proactively or reactively.

The prefrontal cortex also may affect hippocampal activity via the thalamic nucleus reuiens (RE). Under this *thalamo-hippocampal modulation hypothesis* (Fig. 5b), ACC suppresses hippocampal activity via the RE. ACC robustly connects with RE, bidirectionally[273,274]; in turn, the RE originates a major thalamic input to the MTL. In rats, reuniens pathways terminate along the entire septotemporal (dorsoventral) extent of CA1 and the subicular cortices and all layers of ecto-, peri- and entorhinal cortices[275–280]. Recent work indicates that RE projections primarily target hippocampal interneurons[281]. Thus, ACC signals may suppress hippocampal dynamics via RE interactions with inhibitory targets, especially in CA1. Moreover, they proposed that thalamo-hippocampal modulation *reactively controls* intrusion activity, after entorhinal gating fails (Fig. 5c). RE's anatomical projections suggest that this reactive influence could broadly impact MTL, affecting the hippocampus, entorhinal and perirhinal cortices.

No human neuroscience has yet confirmed whether RE mediates the prefrontal cortex's inhibitory influence on hippocampal activity. Nevertheless, rodent fear extinction studies support this hypothesis. Although fear extinction is often viewed as associative learning, retrieval stopping may contribute[114]. According to this retrieval stopping model, extinction trials motivate rats to stop fear memory retrieval. This arises when rats decide, after several extinction trials, that the threat has ceased, prompting fear memory suppression so normal behaviour may resume. Given this model, rodent fear extinction research supports thalamo-hippocampal modulation[282]. Ramanathan and colleagues[283] revealed that RE cells increase firing during

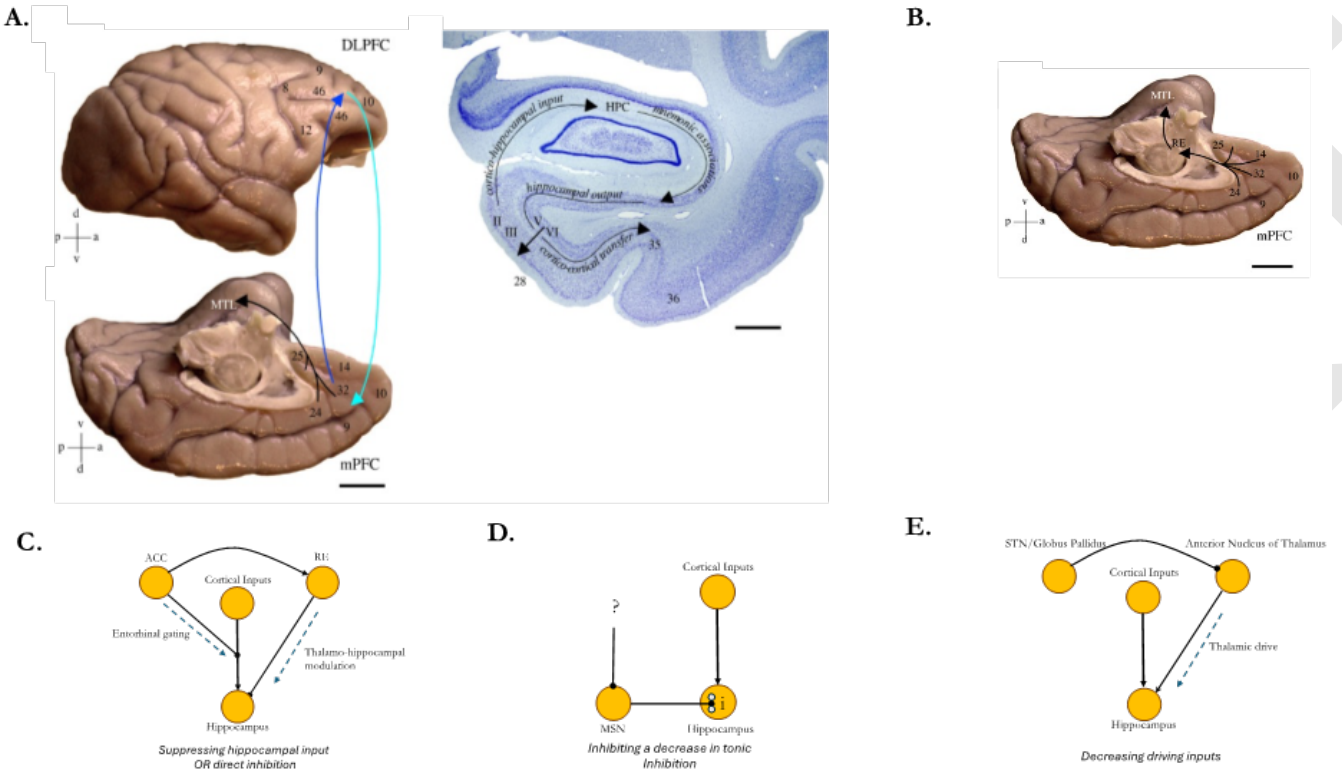


Figure 5. Candidate pathways underlying fronto-temporal inhibitory control. In the dual-pathway hypothesis[166], right aDLPFC and rVLPFC can stop retrieval by driving ACC activity to achieve two outcomes. First, by entorhinal gating **(a)** which prevents cortical cue input from reaching the hippocampus. Entorhinal gating happens when ACC projections to deep layers of the entorhinal cortex terminate on inhibitory interneurons, whose activity interrupts cue input arriving via superficial layers (right side, panel a). In the second pathway, ACC projections to the Nucleus Reuniens of the thalamus can initiate inhibitory inputs from that structure to the hippocampus, suppressing its activity and terminating retrieval. **c**, A schematic illustrating the distinct actions of entorhinal gating and thalamo-hippocampal modulation, via the RE, which operate by truncating hippocampal input or suppressing hippocampal activity. **d**, A schematic of the medial septal pacemaker suppression hypothesis. This hypothesis proposes that the right aDLPFC (via pathways yet to be identified, represented by a question mark), suppress activity in the medial septal nucleus in a sustained manner. This suppression interrupts the action of long-range medial-septal GABAergic inputs into the hippocampus (and cholinergic inputs). Because long-range medial-septal inhibitory inputs terminate on GABAergic hippocampal interneurons, hippocampal tonic inhibition increases, impairing memory function, terminating unwelcome thoughts that rely on hippocampal activity. **e**, A schematic of the thalamic input suppression hypothesis. In this hypothesis, hippocampal memory processes depend on sustained thalamic drive from the anterior nucleus of the thalamus, which can be interrupted when the subthalamic nucleus inhibits this structure (via effects on Globus Pallidus and Substantia Nigra).

extinction recall, which could suppress hippocampal activity. Moreover, RE inactivation impaired extinction learning and its later expression, consistent with its predicted role in inhibiting fear memory. Chemogenetically silencing prefrontal neurons projecting to RE also impairs extinction memory expression. Recent work shows that as fear extinction progresses, the prefrontal cortex, RE, and hippocampus exhibit increased theta power and coherence (6-8 Hz), indicating fronto-hippocampal communication[284]. Inactivating RE eliminated this coherence, establishing RE's role in fostering communication. Critically, when rats were placed in a novel context after extinction—a situation that usually triggers fear's return—8 Hz stimulation of RE eliminated this effect, showing RE's causal role in suppressing fear memories. Confirming this possibility, inactivating RE-CA1 projections following contextual fear conditioning lengthens fear responses to the conditioned context and delays extinction[285]. Thus, RE mediates fear memory suppression in the hippocampus, fitting a broader role in suppressing unwanted thoughts.

Medial Septal Pacemaker Suppression

Projections from the medial septal nucleus (MSN) in the basal forebrain may increase hippocampal GABAergic activity, downregulating this structure[67]. Specifically, hippocampal downregulation during suppression may reflect increased tonic inhibition of hippocampal principal cells via sustained disinhibition of GABAergic interneurons. What "disinhibits" hippocampal interneurons"? Many hippocampal interneurons (which are GABAergic) undergo long-range rhythmic inhibition from GABAergic pacemaker cells projecting from the MSN[191,286–288]. These septo-hippocampal inputs, together with hippocampo-septal back-projections, drive theta activity essential for encoding and retrieval[286,287,289]. Strikingly, lesions to/inactivation of the MSN desynchronizes hippocampal rhythms, reduces overall EEG amplitude, abolishes hippocampal theta, and impairs episodic memory[290]. These outcomes arise in part because disrupting the MSN eliminates inhibitory septo-hippocampal inputs, disinhibiting hippocampal interneurons, increasing their tonic inhibi-

tion of principal cells[291]. Thus, inhibiting MSN may suppress hippocampal activity so that unwanted information can be disregarded (Fig. 5d)[292,293].

Supporting this hypothesis, suppressing unwanted thoughts down-regulates MSN activity[67], providing the first human evidence that MSN suppression may disrupt hippocampal function. Whether these regions interact during suppression, however, remains unexamined. This MSN suppression hypothesis converges with evidence that retrieval stopping reduces medial-temporal lobe theta-power[66,148] and induces an amnesic shadow that disrupts hippocampal function[125,177,178]. Thus, the fronto-temporal inhibitory control pathway may include a signal that suppresses pacemaker cells in the MSN, increasing tonic inhibition of hippocampal principal cells.

Input Suppression via the Subthalamic Nucleus

Stopping unwanted thoughts may involve fronto-subthalamic and fronto-striatal mechanisms critical to stopping actions. Rapidly cancelling actions recruits a monosynaptic "hyper-direct" connection from the prefrontal cortex to the *subthalamic nucleus* (STN) that can, via downstream impact on the internal globus pallidus and substantia nigra pars reticulata, suppress thalamo-cortical drive into the motor cortex[11,168–170]. This rapid-acting stopping mechanism cancels all actions regardless of effector, by eliminating necessary thalamo-motor drive globally. Thus, this *hyper-direct pathway* operates via STN-mediated input suppression. Unlike this rapid global mechanism, the *indirect pathway* through the caudate/putamen mediates a slower, selective inhibition of to-be-stopped actions, achieved with targeted input suppression[294,295]. This latter pathway depends on the caudate/putamen[296–299].

Retrieval stopping also engages the STN and basal ganglia. Meta-analyses indicate that action and retrieval stopping activate a co-localized region in the right caudate/putamen[93] suggesting that this region's function generalizes to thoughts. Wessel and Anderson[11] hypothesized that retrieval stopping exploits input suppression as with action stopping. This mechanism could work in several ways: by preventing sensory input from initiating hippocampal retrieval; by gating retrieved content out of working memory after hippocampal retrieval has occurred[300] (perhaps suppressing thalamic drive to neocortical representations); or, by suppressing thalamic drive into the hippocampus itself. Just as the ventral thalamic motor segments sustain thalamo-cortical drive to motor cortex, other thalamic nuclei sustain drive to regions providing input to or receiving output from the hippocampus, or even to the hippocampus (e.g., the anterior nucleus of the thalamus). And, just as the STN and caudate/putamen contribute to suppressing thalamo-cortical drive to motor cortex, they may, via suppressing thalamic nuclei, interrupt it for memory. This hypothesis need not posit active inhibition of memories in hippocampus or cortex, but rather rapid termination of driving input to those regions (Fig. 5d). Thus, this mechanism may be better suited to explaining the momentary regulation of awareness than forgetting.

Mental Health Implications of the Fronto-Temporal Inhibitory Control Pathway

The fronto-temporal inhibitory control pathway offers a neurocognitive framework for understanding perseverative, intrusive, and compulsive thinking and the mechanisms underlying mental-health treatments. This framework moves beyond broad discussions of executive function's mental-health role by specifying the mechanisms of a well-defined mental process, deficits in which may underpin a hallmark feature of psychiatric illnesses: intrusive thinking.

Intrusive thoughts pervade psychiatric conditions, with intrusion content varying by disorder[14,243,257,301–305]. Although specialized models exist for intrusive memories, pathological worries, obsessions, ruminations, and cravings[14,306,307], involuntary retrieval unifies these phenomena (Fig. 1c). For example, fearful images about the future do not refer to lived experiences but are scenarios, constructed by hippocampal processes[308,309]. Similarly, rumination, including elaborate self-criticism, imagined arguments or counterfactual thinking about grievances, recruits hippocampally-mediated scenario construction[308]. Even retrieving general ideas activates networks overlapping those supporting episodic retrieval[20,21]. Thus, whether intrusions concern the past or future[235], the real or hypothetical, or general thoughts or specific events, the fronto-temporal pathway may stop their retrieval. If so, diverse intrusive symptoms may arise from a *transdiagnostic retrieval stopping deficit*[310]. Supporting this hypothesis, compromised retrieval stopping arises across psychiatric disorders[311]. PTSD is associated with diminished SIF on direct[163,312] and indirect memory tests[51], reduced hippocampal or neocortical modulation by right aDLPFC[47,51,75] and aberrant predictive control of the fronto-temporal pathway[313]. Participants with depression[314–316], anxiety[317] and ruminative thinking[61,318] show reduced SIF. State variables affected in psychiatric conditions also compromise the fronto-temporal inhibitory control pathway, including stress and sleep deprivation[37,49,319–322]. A transdiagnostic retrieval stopping deficit may explain evidence for a dominant psychometric dimension of vulnerability to psychiatric illness, known as "p"[323] (analogous to the psychometric dimension of intelligence, "g"). Indeed, *p* is related to a task-general executive function component, a component hypothesized to reflect inhibitory control[107] that requires the right aDLPFC region discussed here[106] (Fig. 3).

Transdiagnostic retrieval stopping deficits could originate not only from right aDLPFC or VLPFC, but also downstream elements of the fronto-temporal pathway. For example, hippocampal GABA deficiency may cause thought stopping deficits (Box 1). However, unlike models focusing on broad executive functions and their prefrontal basis, the current framework allows for thought suppression deficits deriving solely from hippocampal dysfunction. In such

cases, response inhibition assays such as the Stop-Signal or Anti-Saccade tasks, though validly estimating prefrontal contributions, would underestimate dysfunction. Differential prefrontal or hippocampal contributions could explain why greater SSRT impairments arise for some disorders (ADHD, OCD) than others (e.g., anxiety disorder, major depression)[3], despite thought control deficits in the latter. Thus, the mechanistic specificity of the fronto-temporal pathway model allows it to explain transdiagnostic and disorder-specific origins of intrusive thinking. Indeed, the hippocampus's unique contribution to the fronto-temporal pathway motivates a focus on hippocampal GABAergic function as a drug treatment target for improving the regulation of unwanted thoughts, an opportunity missed by focusing on response inhibition or general executive function.

The current framework also suggests mechanisms underlying therapeutic benefits that can be leveraged to improve interventions. For example, fear extinction processes are deficient in anxiety, PTSD and OCD[324–327]. Yet, despite progress understanding fear extinction's neurobiology, few novel PTSD treatments have emerged[328]. One problem lies in the failure to exploit higher cognition's contribution to extinction. For example, promoting retrieval stopping may benefit extinction, improving its durability and generalization[329]. Practice could repeatedly present participant-designed fear reminders in a TNT task that suppressed fearful imagery[235]. Indeed, training people to stop retrieval of recurring fears improved mental health, including depression, worry, and anxiety (Box 2), suggesting that retrieval stopping supports resilience[51,322,330] perhaps in part by active forgetting[32,331]. Moreover, extinction-based therapies, such as exposure therapy, may work because repeatedly exposing feared stimuli builds suppression skill; combining exposure with retrieval stopping training may increase exposure's effectiveness. Other interventions that train people to regulate thoughts through meditation, or cognitive behavioral techniques may capitalize on retrieval stopping. The present model offers a fertile framework for understanding and improving existing and emerging therapies[332].

Concluding Remarks

We have presented the evidence for a fronto-temporal inhibitory control pathway that is critical to stopping unwelcome thoughts. This pathway differs from that involved in response inhibition, despite homologies in the processes of stopping thoughts and actions. Suppressing thoughts across diverse content[32,39–41] shares domain-general stopping processes mediated by right aDLPFC and VLPFC, but it instead down-regulates hippocampal activity to interrupt retrieval, and forget the expelled thought. Intrusions of unwanted content strongly engage this pathway, consistent with a role in retrieval cancellation[15,33,48,51]. Retrieval stopping indices have been associated with trait anxiety, PTSD symptoms, rumination, and thought control ability[311], and behavioral and ERP suppression measures predict upsetting intrusion frequency after analogue trauma[99].

This fronto-temporal inhibitory control pathway offers advantages over motor response inhibition as a model system for studying the pathophysiology of intrusive thoughts. For example, hippocampal down-regulation during thought suppression led us to identify hippocampal GABAergic inhibition as a distinct thought suppression parameter. A novel focus on hippocampal GABA integrates inhibitory control of thought with rodent models of anxiety disorders, schizophrenia, PTSD, and depression, which often hypothesize hippocampal GABAergic dysfunction as part of disease pathophysiology. How prefrontal control modulates hippocampal interneuron networks remains to be established. Hippocampal disinhibition may underlie aberrations in default network suppression in psychiatric disorders and explain why this network dynamic accompanies intrusive symptomatology. Understanding the mechanisms of inhibitory control over thought will yield a theoretically precise model of core psychological processes in intrusive thinking, to inform the development and optimization of treatments of common mental-health conditions.

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The authors declare no competing interests.

Author Contributions

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