

REPORTS

Lipoxygenases are nonheme, iron-containing enzymes that catalyze the oxygenation of certain polyunsaturated fatty acids, such as lipids and lipoproteins. 15-Lipoxygenase has been implicated in the pathogenesis of several diseases, including atherosclerosis (15), asthma (16), cancer (17), and glomerulonephritis (18). The biological functions of murine or human 15-LO have not yet been determined with certainty. Nevertheless, there is accumulating evidence to suggest a potential mechanism by which overexpression of 12/15-LO could exert a negative effect on skeletal development. Pluripotent marrow stromal cells can differentiate into one of several mature forms including adipocytes and osteoblasts, a process regulated by both protein and lipid factors. In many instances, lipid regulation of differentiation is mediated through PPAR-dependent signaling pathways. Linoleate is the most abundant fatty acid in low density lipoprotein (LDL) and is thought to be the largest reservoir of 12/15-LO substrate. Oxidized LDLs serve as PPAR γ ligands (19) and have been shown to activate CD36 expression (20). Furthermore, oxidized lipids inhibit osteoblastic differentiation from preosteoblasts in vitro (21, 22) and bone formation in vivo (23). In addition, 5-lipoxygenase metabolites of arachidonic acid inhibit bone formation in vitro (24) and 5-LO-deficient mice exhibit increased cortical thickness (25); however, no BMD QTL has been identified on chromosome 6 where *Alox5* resides.

The identification of *Alox15* as a susceptibility gene for peak BMD in mice may have relevance to human osteoporosis. An autosomal genome screen for spinal BMD in 17 extended pedigrees found linkage to a chromosomal region (17p13.1) containing the genes encoding human 12-LO and 15-LO (26). In addition, an association between a single-nucleotide polymorphism of PPAR γ and BMD was identified in postmenopausal women (27). Further studies in both animal models and human populations will be required to gain a deeper understanding of the role the 12/15-LO pathway plays in processes leading to peak bone mass attainment. If 12/15-LO is confirmed to contribute to human osteoporosis risk, inhibitors of the enzyme may merit investigation as a treatment for osteoporosis. Such inhibitors have already been developed for other indications (14).

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Materials and Methods

Figs. S1 and S2

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Neural Systems Underlying the Suppression of Unwanted Memories

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Over a century ago, Freud proposed that unwanted memories can be excluded from awareness, a process called repression. It is unknown, however, how repression occurs in the brain. We used functional magnetic resonance imaging to identify the neural systems involved in keeping unwanted memories out of awareness. Controlling unwanted memories was associated with increased dorsolateral prefrontal activation, reduced hippocampal activation, and impaired retention of those memories. Both prefrontal cortical and right hippocampal activations predicted the magnitude of forgetting. These results confirm the existence of an active forgetting process and establish a neurobiological model for guiding inquiry into motivated forgetting.

Stopping retrieval of an unwanted memory impairs its later retention (1), and this provides a psychological model for the voluntary form of repression (suppression) proposed by Freud (2, 3). Two brain regions that may play important roles in the neurobiological mechanism of memory suppression are the hippocampus and lateral prefrontal cortex. The hippocampus is essential for declarative memory formation (4), and increased hippocampal activation is associated with successful memory formation (5, 6) and the subjective experience of recollecting a recent event (7). Memory suppression requires people to override or stop the retrieval process. Lateral prefrontal cortex is involved in stop-

ping prepotent motor responses (8–11), switching task sets (12, 13), and overcoming interference in a range of cognitive tasks (14–17). It may be hypothesized, therefore, that people suppress unwanted memories by recruiting lateral prefrontal cortex to disengage hippocampal processing.

We adapted the think/no-think paradigm developed to study the suppression of unwanted memories (1) for use in an event-related functional magnetic resonance imaging (fMRI) design (Fig. 1A) (18). Subjects learned word pairs (e.g., Ordeal Roach) and then performed a think/no-think task while being scanned. On each trial, subjects were presented with one member of a pair (e.g., Ordeal) and asked either to recall and think about the associated response (e.g., Roach) (Respond condition) or to prevent the associated word from entering consciousness at all (Suppression condition) for the entire four seconds that the stimulus was presented.

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After scanning, subjects were tested to determine whether attempts to stop retrieval during Suppression trials had impaired memory for the response, when given the originally trained cue (Same Probe test, or SP test). Suppression did impair memory, as cued recall for Suppression items was inferior to recall of Baseline items that did not appear during scanning (Fig. 1B). Further, this memory inhibition effect for Suppression items generalized to novel test cues (independent probe, or IP test), indicating that disrupted memory was unlikely to be due to unlearning of the association linking the trained cue (e.g., Ordeal) to the response (Roach) or to interference from competing associates to the trained cue. Rather, forgetting reflects inhibition of the response (e.g., Roach) (1, 19). Thus, suppression during scanning made subjects unable to recollect memories that had been formed before scanning, and this memory deficit was beyond what was measured for simple forgetting over time.

To identify neural systems involved in suppression, we contrasted activation during Suppression and Respond trials (Fig. 2). A network of brain regions was more active during suppression than during retrieval, including bilateral dorsolateral and ventrolateral prefrontal cortex (DLPFC and VLPFC, respectively; Brodmann's area (BA) 45/46, stronger on left); anterior cingulate cortex (ACC; BA 32); the contiguous pre-supplementary motor area (preSMA; BA 6), a lateral premotor area in the rostral portion of the dorsal premotor cortex (PMDr; BA 6/9); and the intraparietal sulcus (IPS; BA 7) (also in bilateral BA 47/BA 13, and right putamen). The large number of prefrontal regions more active for stopping rather than achieving memory retrieval supports the view that suppression is an active process recruiting brain regions known to be important for executive control functions, such as stopping prepotent motor responses (8, 9).

Suppressing recollection reduced activation bilaterally in the hippocampus (Fig. 2), relative to recollection. Reduced hippocampal activation remained significant after small-volume correction (using anatomically defined regions of interest (ROIs): left hippocampus, $P = 0.006$; right, $P = 0.043$; at the voxel level). Other regions with reduced activation during suppression included bilateral frontal polar cortex (BA 9, right BA 10), posterior insula (BA 13), left parietal cortex (BA 40), and bilateral cuneus (BA 18/17).

Hippocampal activation indexes recollection (7), therefore reduced hippocampal activation in the Suppression condition indicates that subjects successfully stopped or reduced recollection of unwanted memories during scanning. One possibility is that the hippocampus was simply disengaged during Suppression trials,

perhaps because retrieval mode (20) had been terminated by response-override mechanisms. Alternatively, control mechanisms may have interacted with the hippocampus during Suppression trials in a way that impaired later memory. If so, hippocampal activation during Suppression trials should be related to memory inhibition and should be predicted by activation in prefrontal regions involved in producing inhibition effects.

We examined whether there were brain regions in which activation predicted individual differences in the capacity to inhibit unwanted memories. Subjects varied widely in memory inhibition (range, 8% facilitation to 32% inhibition), and this variation may reveal brain regions important to producing this effect. Regression analysis revealed that increased activation in bilateral DLPFC (BA 9/46; anterior to the region found in the overall contrast) predicted increased memory inhibition (Fig. 3, A and

B), as did activation in left VLPFC (BA 44) and in a subset of suppression-related activations, including preSMA, PMDr, and IPS (21). DLPFC activation was related to memory inhibition on both the SP and IP tests (Fig. 3C). The association between DLPFC activation and memory inhibition on the IP test, which is particularly diagnostic of inhibition (1, 19), indicates that DLPFC contributes to inhibiting distracting traces (Fig. 3, A and B) (14, 15). This converges with work showing that lesions to the prefrontal cortex disrupt memory inhibition (22).

Next, we examined whether hippocampal activation was modulated during Suppression trials to produce memory inhibition. We performed a subsequent forgetting analysis to determine whether forgetting that arises in the Suppression condition was associated with a distinctive pattern of hippocampal activation, as compared with normal forgetting for nonsuppressed (i.e., Re-

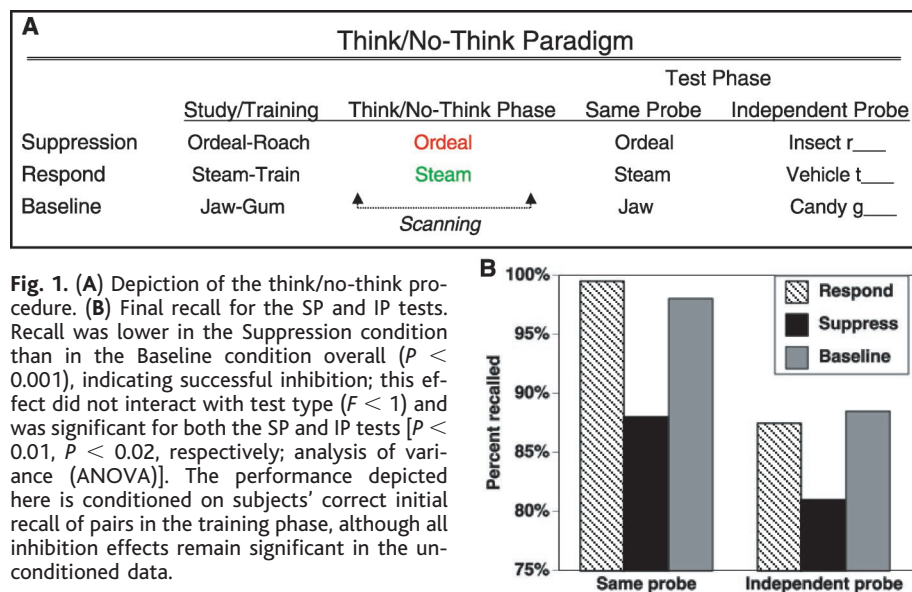
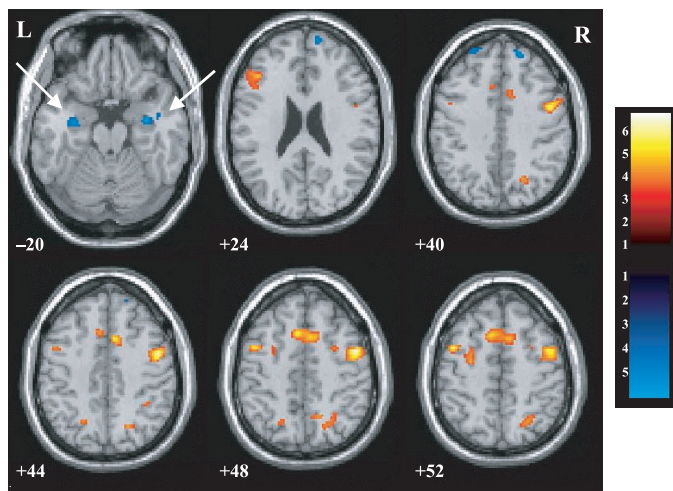


Fig. 1. (A) Depiction of the think/no-think procedure. (B) Final recall for the SP and IP tests. Recall was lower in the Suppression condition than in the Baseline condition overall ($P < 0.001$), indicating successful inhibition; this effect did not interact with test type ($F < 1$) and was significant for both the SP and IP tests [$P < 0.01$, $P < 0.02$, respectively; analysis of variance (ANOVA)]. The performance depicted here is conditioned on subjects' correct initial recall of pairs in the training phase, although all inhibition effects remain significant in the unconditioned data.

Fig. 2. Activation for Suppression trials compared with Respond trials during the think/no-think phase ($n = 24$). Areas in yellow were more active during Suppression trials than during Respond trials, whereas areas in blue were less active during Suppression ($P < 0.001$, uncorrected). Only scanning trials for items learned initially were included in this analysis, although all activations reported here remain significant in the unconditioned image data ($P < 0.001$, uncorrected). White arrows highlight hippocampal deactivation in the Suppression condition.



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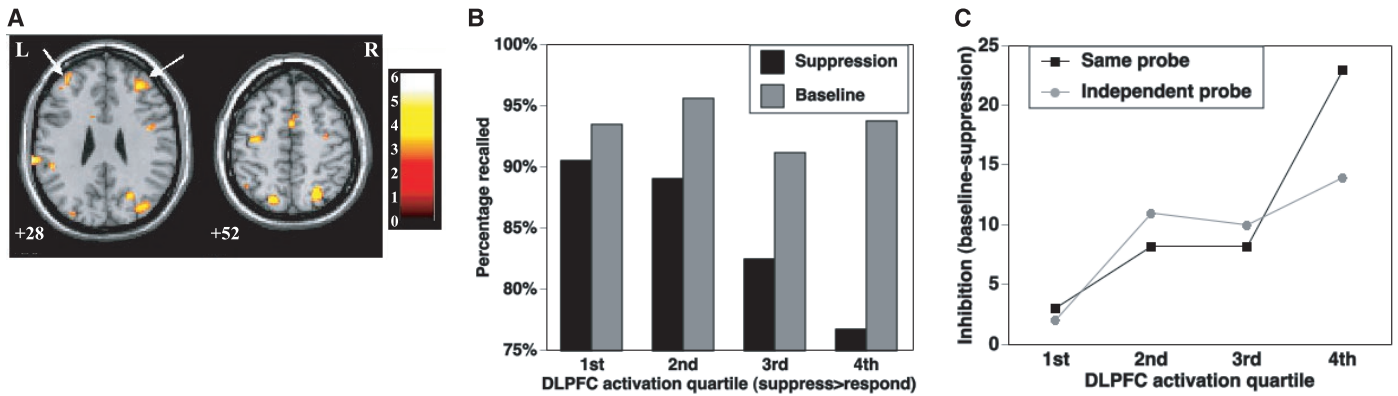


Fig. 3. Relation of Suppression activations to memory inhibition. (A) Suppression-related areas that predict memory inhibition ($n = 24$). White arrows highlight DLPFC regions from the regression analysis that also predict hippocampal activation for Suppression items in Fig. 4. (B) Memory inhibition effects for four subject groups, differing in DLPFC

activation. Increasing DLPFC activation predicts reduced Suppression item recall, but leaves Baseline items unaffected. (C) Memory inhibition for the DLPFC groups, by test type. Inhibition interacted with DLPFC activation group (low versus high DLPFC, $P < 0.05$), and this effect did not interact with test type.

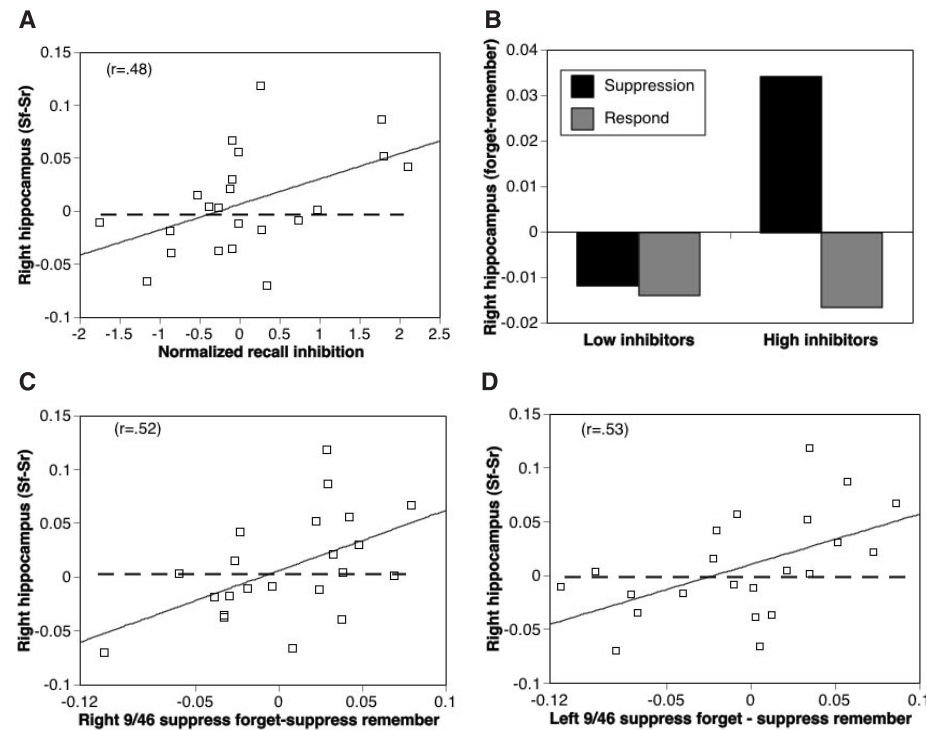


Fig. 4. A subsequent forgetting analysis for Suppression items, focused on functionally defined ROIs in the hippocampus and DLPFC. (A) The difference in right hippocampal activation for Sf and Sr items correlates with memory inhibition, $P < 0.05$. Increasing z scores represent increasing inhibition. (B) Right hippocampal activation differences between forgotten and remembered items in the Respond and Suppression conditions in two inhibition groups. (C) Increased right hippocampal activation for Sf items correlates with increased activation for Sf items, relative to Sr items in right DLPFC, $P < 0.05$. (D) The same correlation as in (C), but with left DLPFC, $P < 0.05$.

respond) items. Forgotten and remembered items exhibited different patterns of activation in the Suppression and Respond conditions: in the Respond condition, items that were later remembered (Rr items) yielded relatively more activation than items that were later forgotten (Rf items), consistent with past findings (5–6, 23). The opposite tendency was observed in the Suppression condition. The interaction of memory status (forget versus remember)

and item type (Suppression versus Respond) was significant in the right hippocampus ($P < 0.05$), indicating that hippocampal activation is differently related to simple forgetting (Respond items) than it is to suppression-induced forgetting.

To further examine whether greater hippocampal activation for Suppression items that were forgotten (Sf items) was linked to memory inhibition, we correlated the amount of memory inhibition subjects exhibited with the activation

advantage for Sf items. The more memory inhibition subjects showed, the greater the hippocampal activation advantage for Sf items relative to suppression items that were remembered (Sr items) (left, right hippocampus, each $P < 0.05$; Fig. 4A). For high inhibitors, Sf items exhibited significantly more activation than Sr items ($P < 0.05$, Fig. 4B).

Increased hippocampal activation in this and prior studies has been associated with accurate memory retrieval, providing a framework for interpreting greater hippocampal activation for suppression items that were forgotten than suppression items that were later remembered. Increased Sf activation may reflect momentary intrusions (inadvertent recollections) of Sf items during Suppression trials. These intrusions may have triggered greater executive control to override retrieval and, in turn, greater memory inhibition (24). Indeed, in behavioral studies, little memory inhibition is found for nonintrusive items (25). Although Sf items exhibited greater activation than Sr items, both item types showed less activation than Rr items ($P < 0.005$), suggesting that such intrusions may have been abbreviated by control.

To determine whether greater hippocampal activation for Sf items was associated with increased control, we performed a subsequent forgetting analysis on the DLPFC and related the observed activations to hippocampal activation. The activation difference between Sf and Sr items (Sf-Sr) in the right and left DLPFC predicted increased Sf activation (Sf-Sr) in the right hippocampus [right DLPFC, $P < 0.05$ (Fig. 4C); left DLPFC, $P < 0.05$ (Fig. 4D)]. Neither DLPFC region predicted left hippocampal activation ($P > 0.4$ in all cases). These findings indicate that the hippocampus and DLPFC interact during attempts to suppress recollection of an unwanted experience. This interaction has a clear behavioral consequence—forgetting—that is contrary to the function normally assigned to the hippocampus.

Although we have emphasized the role of DLPFC in suppression, stopping retrieval is a complex act that recruits the full network identified in our overall analysis. This experiment does not identify the contributions of these regions, but research on attention suggests several possibilities. The ACC may play a key role in suppression, signaling the need for control by DLPFC (10) in response to memory intrusions and/or mediating the influence of DLPFC on the medial-temporal lobe (MTL). These possibilities are consistent with the dense bidirectional projections of ACC with MTL structures (26). Activations in the PMDr, pre-SMA, and IPS are often observed when prepotent motor responses need to be overridden (9). However, PMDr and preSMA receive multimodal inputs (27) and are activated by visual selective attention (28) and by purely cognitive tasks that demand updating in memory and require no motor output (27). These considerations indicate that this network serves a general function that may include controlling perceptually and memorially focused attention.

The current findings begin to specify central features of a neurobiological model of memory control that people may use to adapt their mental environment in response to traumatic experiences (1, 29, 30). Although controlling traumatic memories is difficult, intrusive reminders of trauma and the intensity of the associated emotional response to trauma-related stimuli diminish over time for most people (31). This remission may reflect in part the cumulative inhibitory effects of the voluntary suppression mechanism revealed here, perhaps in tandem with systems involved in the extinction of conditioned emotional responses (32) or in the cognitive reappraisal of traumatic memories (33).

Whether suppression can produce complete and lasting amnesia for an unwanted memory remains unknown. However, this work confirms the existence of an active process by which people can prevent awareness of an unwanted past experience and specifies the neural systems that underlie it. This process causes forgetting. Thus, the current findings provide the first neurobiological model of the voluntary form of repression proposed by Freud, a model that integrates this otherwise controversial proposal with widely accepted and fundamental mechanisms for controlling behavior.

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Freud used Repression to refer to both conscious and unconscious acts. We use the term Repression but limit our discussion to its conscious variety.

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Supporting Online Material

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Materials and Methods
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Reflectins: The Unusual Proteins of Squid Reflective Tissues

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A family of unusual proteins is deposited in flat, structural platelets in reflective tissues of the squid *Euprymna scolopes*. These proteins, which we have named reflectins, are encoded by at least six genes in three subfamilies and have no reported homologs outside of squids. Reflectins possess five repeating domains, which are highly conserved among members of the family. The proteins have a very unusual composition, with four relatively rare residues (tyrosine, methionine, arginine, and tryptophan) comprising ~57% of a reflectin, and several common residues (alanine, isoleucine, leucine, and lysine) occurring in none of the family members. These protein-based reflectors in squids provide a marked example of nanofabrication in animal systems.

The biological world is an arena of nanofabrication, one that can be tapped for information about constraints on the design and production of small-scale materials. Among the most intricate of natural nanoscale materials are those that modulate light, such as the lenses, irises, and reflectors of animals (1).

Reflective tissues are prevalent across the animal kingdom, being particularly conspicuous in species that live in the visually homogeneous pelagic environments of the ocean. In these habitats, reflectors often function in camouflage by modulating incident sunlight or bioluminescence (2, 3).

Reflectivity in animal tissues is achieved by the deposition of flat, insoluble, structural platelets of high refractive index that alternate in layers with materials of low refractive index. This arrangement creates thin-film interference, which results in reflection of some or all of the incident light (4). In aquatic animals, reflector platelets are most often

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