Frontal cortex contributes to human memory formation

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The contribution of medial temporal lobe structures to memory is well established. However recent brain-imaging studies have indicated that frontal cortex may also be involved in human memory formation. Specific frontal areas are recruited during a variety of procedures that promote memory formation, and the laterality of these areas is influenced by the type of information contained in the memory. Imaging methods that capture momentary changes in brain activity have further shown that the likelihood of memory formation correlates with the level of activity in these areas. These results, taken in the context of other studies, suggest that memory formation depends on joint participation of frontal and medial temporal lobe structures.

Primate models of memory and multiple lines of evidence from neuropsychology suggest that medial temporal lobe brain structures are essential for memory formation. Moreover, their function seems to be specific to forms of memory based on conscious reflections of the past, such as those experienced during a recollection of a vivid memory or of a newly learned fact. In contrast, other expressions of memory such as habit formation and skill learning that occur without conscious awareness seem to be independent of medial temporal lobe participation[1–3].

An open question has been how, and to what degree, cortical areas outside the medial temporal lobes contribute to conscious remembering. This review focuses on a set of findings emerging from brain-imaging studies that provide evidence for an important role of frontal regions in memory formation. Like the medial temporal lobes, the frontal lobes seem to be involved in forming memories that support conscious recollection of the past. Furthermore, activity within specific frontal regions correlates with a wide range of behavioral factors that influence memory formation.

Frontal activity during encoding

As might be expected, intentional memorization is a highly effective means of encoding words into long-term memory. Positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) studies consistently demonstrate that specific areas within left frontal cortex are active when subjects intentionally memorize words[4–6]. Brain activity increases most often within posterior regions of frontal cortex near the border between motor and prefrontal cortex (located dorsally along inferior frontal gyrus, near Brodmann's areas 44 and 6) and also within more ventral prefrontal regions (near Brodmann's areas 44, 45 and 47; Fig. 1).

Most instances of memory formation in everyday life, however, occur incidentally, without any intention to remember. How does this happen? Cognitive psychology research suggests that memory formation is a byproduct of certain kinds of information processing. For example, items for which meaning and relationship to other remembered items are elaborated are better remembered than items processed in a shallow fashion where only surface characteristics are examined[7].

Frontal regions active during intentional memorization are also active during behavioral manipulations that incidentally alter the effectiveness of memory encoding. For example, when subjects make meaning-based judgments about words, multiple regions within left frontal cortex are activated. Those words are remembered even though the subjects make no explicit attempt at memorization[8–10]. By contrast, if subjects perform a surface-based task where words are judged, for example, to be in uppercase or lowercase letters, frontal activity is minimal, and the words are most often forgotten[8–10]. Dividing attentional resources also seems to influence memory encoding. When attention is directed away from an item, that item is likely to be forgotten even if a subject is attempting to remember it[11]. Consistent with this behavioral observation, one influential study using PET demonstrated that adding a secondary distracting task during intentional memorization caused brain activity in frontal cortex to diminish and memory to be impaired[12].

Perhaps the strongest evidence for frontal involvement in encoding comes from studies examining event-by-event variance in memorization. In everyday life, some experiences are remembered, whereas others are forgotten. Although the level of meaning-based processing or direction of attention to these various experiences may account for a portion of this variability, it is often unclear what makes a particular experience memorable. This issue was initially addressed by electrical scalp-recording techniques. When scalp potentials of subjects were recorded at the time of memorization, distinct neural signatures were noted for words that were later remembered as compared to those for words later forgotten[13,14] (reviewed in ref. 15). Recent developments in fMRI methods[16–20] have allowed the same phenomenon to be examined with more precise spatial localization within the brain (Fig. 3). Such procedures show that, on average, the level of activity within frontal cortex can predict whether an item will later be remembered or forgotten. This is true of both words[10] and picture scenes[21]. These findings strongly suggest that frontal activity can be influenced by (or influences) subtle differences between events that affect memory encoding.

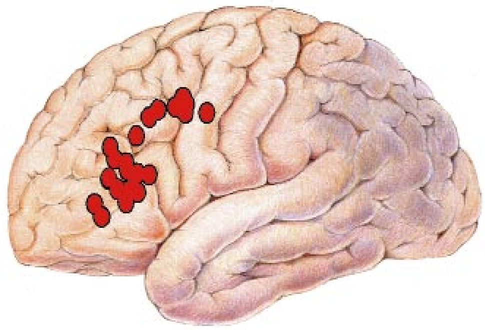

Fig. 1. A lateral view of the human brain schematically illustrates frontal regions active during tasks that promote memorization of verbal materials. These regions may be involved in memory encoding. A number of studies exploring intentional and incidental encoding as well as their event-by-event variances converge to show that activity within these frontal regions correlates with high levels of memory performance.

Frontal involvement in nonverbal memory

So far, we have focused on processing of words. Left frontal cortex has been consistently associated with encoding of verbal materials[22]. However, we are also able to remember aspects of events that are not purely verbal in nature, such as a tune on the radio or the appearance of a neighbor's dog. How are these kinds of information remembered? Cognitive psychologists have long believed that memory formation relies on multiple streams of information, most often distinguished as verbal and nonverbal codes. The most compelling behavioral evidence for this possibility is the finding that a picture of an object such as a dog is more likely to be remembered than the presentation of the word "dog". The implication is that pictures are associated with both nonverbal (image-based) and verbal codes, whereas words are associated with only a verbal code[23,24].

Further evidence that multiple codes contribute to memory processes comes from studies of brain-damaged patients[25–28]. These studies suggest that verbal and nonverbal codes may be processed in different hemispheres. For example, 'split-brain' patients—epileptic individuals who have had communication between their cerebral hemispheres disrupted to minimize the spread of seizure activity—perform significantly better on tests of face memorization when the faces are presented to the right hemisphere rather than to the left hemisphere[26]

In addition, memorization of materials associated with different codes can activate distinct regions of left and right frontal cortex (Fig. 2). Memorization of unfamiliar faces[6] and texture patterns[29], neither of which can be easily associated with a verbal label, activate right frontal regions. Of particular interest is the finding that memorization of nameable objects—items that can be associated with both verbal- and nonverbal imagery-based codes—often elicits bilateral activation of frontal cortex[6]. An intriguing interpretation of this finding is that distinct regions of frontal cortex will, for a single event, code the multiple kinds of information available.

Lateral differences are also noted across the event-by-event studies discussed above. Left frontal activity predicted which words would be remembered[10], whereas right frontal activity predicted which picture scenes would be remembered[21]. Taken together, these studies suggest that, depending on the kind of information being memorized, multiple lateralized regions within frontal cortex may participate in encoding.

Moreover, experimental conditions can also affect the lateralization of regions engaged during memory formation. For example, left frontal activity is observed during memorization of faces under conditions where long intervals occur between face presentations[30,31]. Verbal encoding operations that rely on left frontal activity may be more accessible under these conditions, although this possibility has not yet been tested directly.

Frontal cortex damage

Despite the support for a role of frontal cortex in encoding from brain-imaging studies, its implication in memory formation by studies of brain-damaged patients is less clear. Memory disturbances following frontal damage have been noted to varying degrees, depending on the exact kind of memory test. In particular, memory difficulties are observed in frontal patients when the test requires recollection of a particular context (for example, remembering who made a particular statement) or judgment of the timing of an event[32–34]. However, patients with frontal damage often perform well on many other tests of memory, such as simple recognition of past items. Preservation of certain memory abilities following frontal damage has often been contrasted to the profound amnesia that can follow damage to the medial temporal lobes.

There are several possible explanations for this apparent incongruity. First, left and right frontal regions seem to be used for different materials, strategies and contexts. Thus, for limited unilateral lesions, remaining frontal regions either in the same or opposite hemisphere may be able to overcome difficulties in many encoding situations. Similarly, in medial temporal injury, damage usually must be bilateral to produce profound memory deficits.

Second, regions related to memory encoding do not exist solely to encode information for later retrieval. Rather, the function of certain frontal regions may concurrently relate to both memory encoding and immediate task demands. Frontal cortex is implicated in a variety of functions, including higher-level thought and planning[35,36]. Several hypotheses propose that certain regions within frontal cortex participate in short-term maintenance and manipulation of information, which are essential to many kinds of information-processing tasks. One possibility is that frontal cortex may serve as an internal buffer, allowing manipulation of information and, in turn, selection among possible responses to that information[36–38]. The dual nature of this processing presents a formidable challenge to the study of memory formation. Memory encoding may be the eventual byproduct of information processing engaged by the frontal lobes for other reasons. By this view, a single processing event may have two quite distinct effects. The first is observed during the event and relates to immediate task completion (for example, working-memory judgment or word generation). The second effect is observed tangentially but lies at

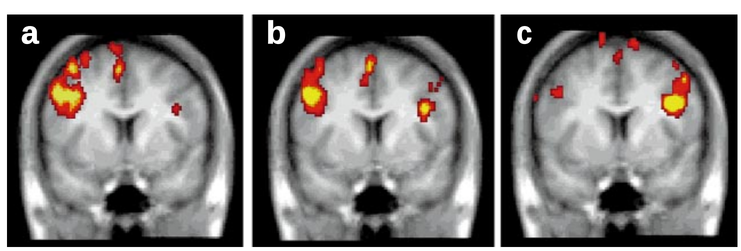

Fig. 2. Frontal regions active during memory encoding may depend on the materials being memorized. Data revealing lateralization differences across verbal (words) and non-verbal (faces) materials. **(a)** Words activate left frontal cortex, whereas **(c)** faces activate right frontal cortex. By contrast, **(c)** objects (associated with both an image and a name) activate both right and left frontal cortex. The data[6] show fMRI activity in coronal sections associated with intentional encoding of different materials.

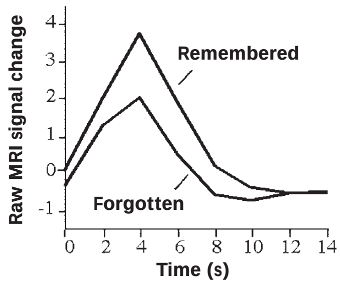

Fig. 3. Activity within frontal regions can predict which items will be remembered or forgotten. Depicted is the fMRI signal from a left dorsal frontal region during an incidental memory encoding task. The data[10] were divided based on subsequent memory performance such that the brain activity associated with later-remembered words could be separated from activity associated with later-forgotten words.

the heart of long-term memory encoding: a process engaged to deal with present task demands initiates a cascade of events that forms a memory for that episode. Thus, processing events associated with frontal activity promote memory formation even though much of the activity may arise for reasons other than intentional memorization. Because memory studies that use brain-damaged patients often exclude patients with specific verbal processing deficits, there may be a 'catch-22' in trying to associate memory function with frontal injury. Given the possible dual function of frontal activity, frontal lesions that produce speech and verbal fluency impairments may also have important but often-overlooked effects on memory encoding[39]. In two telling studies, patients with speech and fluency difficulties typical of left frontal damage did poorly on recognition tests of studied words[40,41]. Both studies also included patients with deficits likely arising from damage to similar regions in the right hemisphere. These patients were impaired at remembering items associated with nonverbal codes including pictures[40,41] and birdsongs[40].

Relation to the medial temporal lobe

One obvious issue to be raised at this point is the relation between frontal and medial temporal regions. Damage to the medial temporal lobes is often associated with nearly complete or partial loss of the ability to remember new experiences in the presence of relatively intact cognitive functioning in other domains (for example, see refs. 1, 2 and 42). Memory disturbances noted early in the progression of Alzheimer's disease are associated with pathology in this region[43–45]. Similarly, non-human primate models of memory loss suggest the lesion location for producing memory impairment falls within the hippocampus and adjacent cortex (within the medial temporal lobes)[46,47]. These data convincingly demonstrate that medial temporal lobe regions are critical for memory formation.

Despite the accumulation of evidence from other methods, medial temporal lobe structures remain a somewhat elusive target for brain imaging. Whereas a number of studies observe medial temporal lobe activity during encoding (particularly in the parahippocampal cortex[48]), a number do not—even in the presence of robust activity within frontal cortex[49]. Despite numerous attempts to do so, relatively few studies have reported consistent activity directly within the hippocampus during various task conditions that differ in their ability to promote memory formation.

Nonetheless, how medial temporal and frontal brain regions may jointly participate in memory formation is suggested by data from other sources. Areas within the medial temporal lobes receive inputs from many cortical regions and may contribute to memory formation by associating or 'binding' these inputs with already-present contents of long-term memory[2,50]. According to this view, damage to the medial temporal lobe disrupts memory formation by preventing the construction of novel, often arbitrary, associations that characterize new experiences. Several investigators have noted that the few imaging studies detecting hippocampal activity during memory encoding explore tasks that involve complex new items or associations among items[5,6,48,51–54].

So how does the frontal cortex fit into this picture? One speculation would be that the critical cascade driving human memory formation occurs only when frontal activity provides information to medial temporal lobe structures. The medial temporal lobe may then function to bind together processed information from frontal and other cortical regions to form lasting, recollectable memory traces. Thus, both regions would be critical to the conception of a memory, and lack of participation of either brain region would disrupt memory formation.

A consequence of this hypothesis is that activity within frontal cortex should fail to instill a memory if the medial temporal lobes are damaged. Indeed, this prediction is upheld by recent findings. Patients with amnesia due to medial temporal lobe damage can show normal frontal activity patterns associated with encoding, yet these patients fail to form new memories[49,55]. Correspondingly, as discussed above, normal subjects with intact medial temporal lobes fail to form memories when frontal activity is absent. Thus the interaction of frontal and medial temporal regions, rather than the isolated contribution of either region, seems to be crucial for the effective formation of memories that contribute to consciousness of past events.

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