

The 3-D Prefrontal Cortex: Hemispheric Asymmetries in Prefrontal Activity and Their Relation to Memory Retrieval Processes

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Abstract

■ Neuroimaging results have raised interest in characterizing hemispheric asymmetries in prefrontal activity during different types of memory retrieval tasks. In this issue, Dobbins et al. and Mitchell et al. report results suggesting that the two hemispheres of the prefrontal cortex may indeed make different

contributions to memory retrieval. Here, I discuss these findings within the context of studies characterizing more general processing differences between the cerebral hemispheres and studies characterizing prefrontal organization along the dorsal-ventral and anterior-posterior dimensions. ■

INTRODUCTION

One of the most intriguing questions to emerge from neuroimaging studies of human memory has concerned the existence of functional asymmetries between the left and right hemispheres of the prefrontal cortex (PFC). The question emerged from results of positron emission tomography (PET) studies of verbal memory that repeatedly observed left prefrontal activation during semantic decision tasks and right-lateralized prefrontal activation during tasks that engaged episodic retrieval processes (Tulving, Kapur, Craik, Moscovitch, & Houle, 1994). Reviewing these findings, Tulving et al. (1994) proposed the hemispheric encoding retrieval asymmetry (HERA) model, in which the left PFC was proposed to play a disproportionate role in episodic encoding (via its role in semantic processing) and the right PFC was proposed to play a disproportionate role in episodic retrieval (Tulving et al., 1994). Two years later, Nyberg, Cabeza, and Tulving (1996) summarized a larger number of PET findings that were consistent with the HERA model. Nonetheless, HERA was criticized on a number of levels—one of the most salient criticisms was that in focusing on the left-right dimension, HERA failed to account for perhaps more compelling functional differences along the anterior-posterior and dorsal-ventral dimensions (Buckner, 1996).

More recent functional magnetic resonance imaging (fMRI) and PET studies have generally shown that posterior, ventral PFC areas along the inferior frontal gyrus are robustly recruited during both encoding and retrieval tasks, and that the relative laterality of these

effects is more dependent on the types of material that are being processed than on the type of memory operation (encoding or retrieval) being performed (Golby et al., 2001; McDermott, Buckner, Petersen, Kelley, & Sanders, 1999; Kelley et al., 1998; Wagner et al., 1998). On the other hand, laterality effects in more anterior and dorsal regions of the PFC along the middle and superior frontal gyri remain difficult to characterize. Laterality effects in these regions have typically not varied according to material, but also have not strictly followed predictions of the HERA model. In particular, left and right anterior and dorsolateral PFC subregions are routinely activated during retrieval tasks (Ranganath & Knight, 2003; Nolde, Johnson, & Raye, 1998), leaving open the question of how to characterize laterality effects in these regions.

The studies by Dobbins et al. and Mitchell et al. in this issue represent some of the most theoretically and methodologically sophisticated attempts to address the question of PFC laterality during memory retrieval. Below, I will attempt to provide some additional context for these findings and suggest how they might contribute to a “3-D” characterization of the PFC.

The Left-Right Dimension

Dobbins, Simon, & Schacter (2004) have drawn upon cognitive models suggesting that recognition memory may be supported by two different kinds of information: The assessment of an item's overall familiarity, and recollection of specific aspects of the context in which an item was encountered. The authors propose that the left PFC may disproportionately contribute to the use of specific contextual information to make a memory deci-

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sion, whereas the right PFC may disproportionately contribute to the use of familiarity to make a memory decision. Building on the source monitoring framework introduced by Johnson, Hashtroudi, and Lindsay (1993), Mitchell, Johnson, Raye, and Greene (2004) propose that the left PFC is more engaged during the monitoring of specific memory characteristics, whereas the right PFC is more engaged during the monitoring of undifferentiated information.

Although the views presented by Dobbins et al. (2004) and Mitchell et al. (2004) are not identical, they share many common elements. Both posit a central role for PFC regions during memory tasks that require close monitoring of information during retrieval (see Ranganath & Knight, 2003, for a review). Both models also generate similar predictions—a great deal of behavioral research has shown that the experience of conscious recollection is associated with the successful recovery of specific episodic information (Mather, Henkel, & Johnson, 1997; Norman & Schacter, 1997). In contrast, dual-process models typically treat familiarity as a global assessment of memory “strength” that is insufficient to specify the context of a learning episode (Yonelinas, 2002). Thus, to the extent that one views familiarity as based on assessments of undifferentiated information and recollection as based on assessments of specific information regarding a previous episode (Johnson et al., 1993), the two models are remarkably similar (but see Qin, Raye, Johnson, & Mitchell, 2001, for discussion of differences).

One advantage of the models outlined by Dobbins et al. and Mitchell et al. is that they potentially make contact with global characterizations of relative hemispheric asymmetries in cognition. For example, research on semantic retrieval has indicated that after initial processing of a semantic input, the left hemisphere maintains strong activation of a small set of relevant meanings, whereas the right hemisphere maintains diffuse activation of a much broader range of meanings (Chiarello, Liu, Shears, Quan, & Kacirik, 2003; Beeman et al., 1994). One could speculate that during episodic retrieval, the presentation of a retrieval cue might strongly activate representations of specific attributes of a past event within the left hemisphere. The same cue might diffusely activate a broader range of memory representations in the right hemisphere, and the magnitude of this activation could represent an undifferentiated familiarity signal. Viewed in this way, the proposed specializations of left and right PFC in monitoring specific versus undifferentiated information may fit within an overall pattern of relative processing differences between the two hemispheres.

A second advantage of the models outlined by these researchers is that they generate clear predictions of laterality of PFC activation during different types of memory retrieval tasks. For example, close monitoring of undifferentiated familiarity would be more likely to

support judgments of how many times an item has been encountered (“judgments of frequency,” cf. Hintzman, 1988). Accordingly, judgments of frequency would be expected to elicit right-lateralized PFC activation. Dobbins et al. (2004) found that right PFC regions were disproportionately recruited during judgments of frequency relative to item recognition. In contrast, left PFC regions only exhibited disproportionate activation during judgments of frequency if the retrieval cue was a different exemplar than the studied item. This pattern of results would suggest that the left PFC regions identified by Dobbins et al. were involved in recollecting the specific attributes of each item, rather than familiarity assessment.

Consistent with this idea, Mitchell et al. (2004) suggested that typical source memory decisions requiring close monitoring and evaluation of specific attributes of a study episode (e. g., “Did I see this item or merely hear about it?”) would be expected to elicit left-lateralized PFC activation. Furthermore, these investigators predicted similar lateralized PFC recruitment during memory decisions regardless of whether these decisions concerned active (i.e., maintained in working memory) or inactive (i.e., retrieved from long-term memory) information. This hypothesis was confirmed in the study of Mitchell et al. and accords well with previous neuroimaging studies demonstrating recruitment of the same PFC subregions during working memory and long-term memory decisions (Ranganath, Johnson, & D’Esposito, 2003; Ranganath, Cohen, Dam, & D’Esposito, 2004; Zhang, Leung, & Johnson, 2003; Cabeza, Dolcos, Graham, & Nyberg, 2002).

The findings of Mitchell et al. and Dobbins et al. are difficult to reconcile with other characterizations of laterality within PFC. For example, Cabeza, Locantore, and Anderson (2003) recently proposed that the left PFC is engaged by tasks requiring semantically guided generation of information, whereas the right PFC is engaged by tasks requiring monitoring and checking of retrieved information. However, Cabeza et al.’s “production–monitoring asymmetry” model has difficulty explaining findings of relatively left-lateralized PFC activation during retrieval tasks emphasizing monitoring of specific memory characteristics.

The Dorsal–Ventral and Anterior–Posterior Dimensions

Even if one were to accept the view of PFC laterality advocated by Dobbins et al. and Mitchell et al., there is the question of how to integrate their characterization of the *x* dimension with existing functional characterizations of the *y* and *z* dimensions. Available evidence strongly suggests that the PFC is functionally heterogeneous along these dimensions as well (Buckner, 2003; Ranganath & Knight, 2003). Within the Mitchell et al. study, the PFC regions exhibiting lateralized effects were

generally in posterior dorsal (BA 9) and ventral (BA 45) PFC subregions. Somewhat overlapping regions were identified as showing lateralized effects in the Dobbins et al. study, but in that study, the activation extended anteriorly toward the frontal pole (BA).

How do these different PFC subregions contribute to memory? Consideration of PFC activation in neuroimaging studies across a variety of task domains would suggest that posterior regions of PFC (BA 44, 45, 47) play a role in selecting and inhibiting posterior cortical feature representations relevant to the appropriate memory decision (Buckner, 2003). One can speculate that these types of selection processes should play a vital role in memory retrieval by enhancing the features of a retrieval cue that are most diagnostic for making a memory decision (Dobbins, Foley, Schacter, & Wagner, 2002). For example, the frequency judgment task used by Dobbins et al. would demand selection of familiarity information, whereas the picture–word task used by Mitchell et al. would require selection of visual attributes of the test cue.

It is less clear how more anterior regions of PFC (BA 10 and portions of BA 46) contribute to memory retrieval. These areas are robustly recruited during episodic retrieval tasks (Cabeza & Nyberg, 2000; Duncan & Owen, 2000), but the functions of these regions remain highly controversial (Dobbins, Rice, Wagner, & Schacter, 2003; Ranganath, Johnson, & D'Esposito, 2000; Ranganath & Knight, 2003; Rugg, Henson, & Robb, 2003). I have presented one view, based on the idea that episodic memories are complex and consist of multiple characteristics. In order to make accurate memory decisions, people need to evaluate the match between a retrieval cue and information retrieved from memory along the dimensions that are most diagnostic (Marsh & Hicks, 1998; Mather et al., 1997; Norman & Schacter, 1997; Johnson et al., 1993; Johnson, Kounios, & Nolde, 1997). In previous reports (Ranganath & Knight, 2003; Ranganath et al., 2003; Ranganath & Paller, 1999, 2000), I have proposed, that the anterior PFC is critical for specifying the sources of information that will be diagnostic for making a memory decision (this process has also been described as setting “decision criteria,” “feature weights,” or a “retrieval orientation.” Rugg & Wilding, 2000; Johnson & Raye, 1998; Johnson et al., 1993).

This hypothesis makes specific predictions about the fourth dimension of PFC organization: time. To specify the sources of information that will be relevant for an upcoming memory decision, the anterior PFC should be engaged very early in the retrieval process (i.e., in order to determine how a retrieval cue will be processed). Results from event-related potential (ERP) studies of memory retrieval are consistent with this possibility. In two ERP studies, I compared brain activity between tasks that required subjects to make a general item recognition decision versus tasks that required subjects to make a

recognition decision specifically based on the match between the visual features of test items relative to studied items (Ranganath & Paller, 1999, 2000). Results showed that brain potentials over frontal scalp sites were modulated by the demand to specify the type of information used to make a memory decision, and that these modulations were apparent as early as 200 msec following presentation of a retrieval cue. Results from a parallel fMRI study showed that activity in the left anterior PFC was most sensitive to this manipulation (Ranganath et al., 2000). These findings are consistent with the view that anterior PFC subregions contribute to retrieval by specifying how retrieval cues should be evaluated. Findings from other investigators have been largely consistent with ours and show that anterior PFC activity during source monitoring does not simply reflect task difficulty and is not contingent upon successful retrieval (Fan, Gay Snodgrass, & Bilder, 2003; Dobbins et al., 2002, 2003, 2004; Raye, Johnson, Mitchell, Nolde, & D'Esposito, 2000; Rugg, Fletcher, Chua, & Dolan, 1999; but see also Rugg et al., 2003).

Integrating the ideas described above with those of Dobbins et al. and Mitchell et al., one might propose that the relative laterality of recruitment within anterior PFC should depend on the type of information that should be relevant to an upcoming memory decision—whereas left anterior PFC should be recruited when specific information will be relevant, right anterior PFC should be recruited when undifferentiated familiarity information will be relevant. This proposal is speculative, but it could readily be tested using a combined approach of ERP and fMRI studies to characterize the spatiotemporal dynamics of PFC activity during episodic retrieval.

Conclusions

Clearly, much remains unknown about the functional organization of the PFC and of the processes that different PFC regions may implement. Although different investigators have focused on the dorsal–ventral (D'Esposito & Postle, 2000; Petrides, 1989), anterior–posterior (Ramnani & Owen, 2004; Ranganath & Knight, 2003; Christoff & Gabrieli, 2000), and left–right (Dobbins et al., 2004; Mitchell et al., 2004; Cabeza et al., 2003; Nolde et al., 1998; Tulving et al., 1994) dimensions, a full account of prefrontal functions will likely have to take each of these dimensions into account. Nonetheless, by presenting plausible hypotheses for left–right asymmetries that make contact with more general theories of prefrontal function and hemispheric laterality, Dobbins et al. and Mitchell et al. have made important contributions to the literature.

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