Lateralization of Prefrontal Activity during Episodic Memory Retrieval: Evidence for the Production-Monitoring Hypothesis

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Abstract

■ We propose a new hypothesis concerning the lateralization of prefrontal cortex (PFC) activity during verbal episodic memory retrieval. The hypothesis states that the left PFC is differentially more involved in semantically guided information production than is the right PFC, and that the right PFC is differentially more involved in monitoring and verification than is the left PFC. This "production-monitoring hypothesis" differs from the existing "systematic–heuristic hypothesis," which proposes that the left PFC is primarily involved in systematic retrieval operations, and the right PFC in heuristic retrieval operations. To compare the two hypotheses, we measured PFC activity using positron emission tomography (PET) during the performance of four episodic retrieval tasks: stem cued recall, associative cued recall, context recognition (source memory), and item recognition. Recall tasks emphasized production processes, whereas recognition tasks emphasized monitoring processes. Stem cued recall and context-recognition tasks underscored systematic operations, whereas associative cued recall and item-recognition tasks underscored heuristic operations. Consistent with the production-monitoring hypothesis, the left PFC was more activated for recall than for recognition tasks and the right PFC was more activated for recognition than for recall tasks. Inconsistent with the systematic–heuristic hypothesis, the left PFC was more activated for heuristic than for systematic tasks and the right PFC showed the converse result. Additionally, the study yielded activation differences outside the PFC. In agreement with a previous recall/recognition PET study, anterior cingulate, cerebellar, and striatal regions were more activated for recall than for recognition tasks, and the converse occurred for posterior parietal regions. A right medial temporal lobe region was more activated for stem cued recall and context recognition than for associative cued recall and item recognition, possibly reflecting perceptual integration. In sum, the results provide evidence for the production-monitoring hypothesis and clarify the role of different brain regions typically activated in PET and functional magnetic resonance imaging (fMRI) studies of episodic retrieval. ■

INTRODUCTION

In positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) studies, episodic memory retrieval (Tulving, 1983) is typically associated with activations in prefrontal, medial temporal, parietal, cerebellar regions, and other brain regions (for reviews, see Rugg & Henson, in press; Cabeza & Nyberg, 2000). However, the role of these regions in episodic retrieval remains unclear. Although the right prefrontal cortex (PFC) is generally more involved with episodic retrieval, and the left PFC more involved with episodic encoding and semantic retrieval (as noted by the hemispheric encoding/retrieval asymmetry model, Nyberg, Cabeza, & Tulving, 1996; Tulving, Kapur, Craik, Moscovitch, & Houle, 1994), both right and left PFC are often activated during episodic retrieval tasks. The main goal of the present study was to investigate the differential contributions of left and right PFC to episodic retrieval. Undeniably, an important factor determining the lateralization of PFC activity during episodic retrieval is the verbal versus pictorial nature of the stimuli (McDermott, Buckner, Petersen, Kelley, & Sanders, 1999; Kelley et al., 1998; Wagner et al., 1998). However, the verbal–pictorial dimension is not the only critical factor because a considerable amount of variability in the lateralization PFC activity remains even if one considers only those studies that used verbal stimuli. We propose here that an important factor determining the lateralization of PFC activity during *verbal* episodic retrieval is the proportion of production versus monitoring operations tapped by the task. Below, we explain our production-monitoring hypothesis and describe the rationale of the present study.

Production-Monitoring Hypothesis

Functional neuroimaging studies have strongly linked the left PFC to semantic retrieval (Cabeza & Nyberg,

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2000; for reviews, see Gabrieli, Poldrack, & Desmond, 1998; Wise et al., 1991; Petersen, Fox, Posner, Mintun, & Raichle, 1989), and the role of the left PFC during episodic retrieval has been attributed to semantic and generation operations (Cabeza, Rao, Wagner, Mayer, & Schacter, 2001; Nyberg, Cabeza, et al., 1996). In contrast, the role of the right PFC during episodic retrieval has been attributed to verification and checking operations (Allan, Dolan, Fletcher, & Rugg, 2000; Henson, Shallice, & Dolan, 1999; Fletcher, Shallice, Frith, Frackowiak, & Dolan, 1998; Rugg et al., 1998), which is an idea supported also by lesion evidence (Schacter, Curran, Galluccio, Milberg, & Bates, 1996). Combining these notions, we propose here that during verbal episodic retrieval, the left PFC is differentially more involved in semantically guided information production processes than is the right PFC, whereas the right PFC is differentially more involved in monitoring and verification processes than is the left PFC.

We describe below five assumptions to characterize our view of the production-monitoring distinction.

1. *Differences between recall and recognition tasks*. In general, production processes play a more important role in recall than in recognition tests, whereas monitoring processes play a more important role in recognition than in recall tests (for similar ideas, see Anderson & Bower, 1972; Barhrick, 1969; Kintsch, 1968). In recall tests, retrieval cues provide little information about the targets to be remembered; hence, these cues need to be augmented through the semantically guided production of additional information. In recognition tests, retrieval cues provide rich information about the targets; hence, production processes are not as necessary. Conversely, recognition tests typically include distractor items that must be rejected and, consequently, these tests are critically dependent on monitoring and evaluation processes. In recall tests, distractors are not typically included, and the fact that a candidate target was successfully generated provides some preliminary evidence of its validity, thereby reducing the need for monitoring (Why would it come to mind if I had not seen it?, e.g., Marsh, Landau, & Hicks, 1997; Johnson, Foley, Suengas, & Raye, 1988). Combined with the first assumption, the monitoring-production hypothesis predicts that during episodic retrieval left PFC activity will tend to be greater for recall than for recognition tasks, whereas right PFC activity will tend to be greater for recognition than for recall tasks.

2. *Differences among recall tasks and among recognition tasks.* The first assumption does not imply that the amount of production and monitoring processes is constant across different recall tasks and across different recognition tasks. On the contrary, we assume that different types of recall and different types of recognition differ in terms of the involvement of production and monitoring operations. For example, we assume that associative-recognition and context-recognition tasks involve a greater amount of production processes than item-recognition tasks. In associative-recognition tasks, subjects learn new relationships between pairs of unrelated items (e.g., ''elephant–cruise''), and at test, they recognize word pairs (e.g., ''elephant–strawberry'' must be rejected). Performance in these tasks may involve a generate-to-recognize strategy (e.g., generate ''cruise'' in order to reject ''strawberry''), which depends on production processes. This idea could explain why we did not find the left PFC to be more activated for recall than for associative recognition in a previous PET study (Cabeza, Kapur, et al., 1997). Similarly, since context-recognition tasks involve the production of contextual information and demanding monitoring operations, they are likely to involve greater production and monitoring components than simple item-recognition tasks (Nolde, Johnson, & Raye, 1998; Johnson, Hashtroudi, & Lindsay, 1993).

3. *Differences among production processes and among monitoring processes.* We assume that there are different kinds of production processes and different kinds of monitoring processes, which may involve different subregions within the left and right PFC. These subregions may correspond to different functional areas that PET and fMRI studies have identified within the left (e.g., Poldrack et al., 1999; Kapur et al., 1996; Owen, Evans, & Petrides, 1996) and right (e.g., Henson, Shallice, et al., 1999; Fletcher et al., 1998) PFC.

4. *Independence from level of recovery.* We assume production and monitoring processes may occur regardless of whether the level of memory recovery is high or low. When recovery is low, production processes may contribute to the generation of additional retrieval cues, but when recovery is high, some of the same production processes may contribute to the generation of recovered information. Likewise, when recovery is low, monitoring processes may contribute to the evaluation of the doubtful episodic information, and when recovery is high, they may contribute to the processing of a rich retrieval output. Thus, it is tangential to the production-monitoring hypothesis whether the left PFC is activated during effortful retrieval (Schacter, Alpert, Savage, Rauch, & Albert, 1996; Andreasen, O'Leary, Arndt, et al., 1995; Andreasen, O'Leary, Cizadlo, et al., 1995) or successful recollection (Henson, Rugg, et al., 1999), and whether the right PFC is activated during low confidence recognition (Henson, Rugg, Shallice, & Dolan, 2000) or high target-density conditions (Rugg, Fletcher, Frith, Frackowiak, & Dolan, 1996).

5. *Time course of production and monitoring processes.* Finally, we assume that production processes occur primarily during early (''prerecovery'') and intermediate (''recovery'') phases of retrieval, whereas monitoring processes occur mainly during intermediate and late (''postrecovery'') phases of episodic retrieval. Combined with this assumption, the production-monitoring hypothesis predicts that brain activity measures with

high temporal resolution, such as event-related potentials (ERPs), could detect during the course of retrieval a shift from left to right PFC activity. Consistent with this prediction, a recognition ERP study by Schloerscheidt and Rugg (1997) reported "frontally distributed old/new effects, which shifted over time from a left- to a right-sided maximum" (p. 3281). Moreover, the early left frontal ERP effect tends to be common during recall tasks (Donaldson & Rugg, 1999; Tendolkar, Doyle, & Rugg, 1997), and the late right frontal ERP effect during recognition tasks (for a review, see Allan, Wilding, & Rugg, 1998). Furthermore, a study investigating slow cortical potentials during autobiographical memory found that during an early phase of the retrieval process activity was maximal on left frontal electrodes, but as retrieval progressed, activity began to rise on right frontal electrodes (Conway, Pleydell-Pearce, & Whitecross, 2000).

Rationale

The production-monitoring hypothesis differs from the systematic–heuristic hypothesis proposed by Nolde et al. (1998), which states that the right PFC is more involved in heuristic retrieval processes, whereas the left PFC is more involved in systematic retrieval processes. According to Nolde et al., heuristic processes are sufficient when retrieval tasks are relatively simple, whereas systematic retrieval processes are needed when retrieval tasks require more complex operations, such as self-cueing or deliberate analysis of retrieved information. Consistent with this hypothesis, a meta-analysis of PFC activations in PET/fMRI studies of episodic retrieval showed that PFC activations tend to be right-lateralized for tasks classified as heuristic but bilateral for tasks classified as systematic (Nolde et al., 1998). However, this finding is not inconsistent with the production-monitoring hypothesis, because those tests classified as systematic could have involved a greater production component, and those classified as heuristic, a greater monitoring component. To compare the two hypotheses, it is critical to contrast them directly within subjects and under similar experimental conditions. This was the main goal of the present study.

Using PET, we scanned subjects during four episodic retrieval tasks (see Table 1): stem cued recall (SCR), associative cued recall (ACR), context recognition (CRN), and item recognition (IRN). Before each scan, subjects studied words or word pairs, and during the scan, they performed one of the four tasks. In each trial of the tasks, subjects were presented with a single verbal item and responded by saying one word aloud (see Table 1). In the SCR condition, subjects studied single words, and at test, they recalled a studied word that fitted word stems. In the ACR condition, they studied unrelated word pairs, and at test, they were presented with the first word of each pair and tried to recall the second word. In the study phase of the CRN condition, half of the words were presented visually and half auditorily, and at test, probe words were classified as "seen" or "heard." Finally, the IRN condition was a standard old/new recognition paradigm.

Table 1. Examples of the Four Scanning Conditions

	Study Stimuli	*Test Stimuli*	*Test Responses*
SCR	window	win____	window/pass
ACR	lawyer–window	lawyer	window/pass
CRN	window	window	seen/heard
IRN	window	window	studied/new

Factorial Design	**More Production Processes**	**More Monitoring Processes**
More Systematic Processes	stem cued-recall (SCR)	context recognition (CRN)
More Heuristic Processes	associative cued-recall (ACR)	item recognition (IRN)

Figure 1. Factorial design crossing production-monitoring and systematic–heuristic factors.

As illustrated by Figure 1, the four tests fill the cells of a 2 × 2 matrix crossing production-monitoring and systematic–heuristic factors. As noted above, recall tasks (SCR and ACR) can be assumed to involve a greater production component than recognition tasks, and recognition tasks (CRN and IRN) to involve a greater monitoring component than recall tasks. At the same time, these tasks can be organized along the systematic–heuristic dimension on the basis of criteria proposed by Nolde et al. (1998). As indicated by the headings in Figure 1, these task classifications are relative, not absolute. For example, IRN is less systematic than CRN, but it may be more systematic than forced-choice recognition (Nolde et al., 1998). The relativity of task classifications is not a problem because the predictions investigated are also relative. The fact that the matrix in Figure 1 classifies tasks as having more production or more monitoring processes does not mean that these two types of processes are always inversely related. Production and monitoring are not the endpoints of a single continuum but two different continua, and it is perfectly possible to develop tasks that are high in both or low in both types of processes.

The production-monitoring and systematic–heuristic hypotheses make different predictions regarding the lateralization of PFC activity in comparisons among the tasks in Figure 1. The production-monitoring hypothesis predicts that the lateralization of PFC activity should follow the columns of the matrix: The left PFC should be more activated for recall (SCR/ACR) than for recognition (CRN/IRN) tasks, whereas the right PFC should show the converse pattern. The prediction is not that every single voxel within the left and right PFC will show a significant difference in activation across tests, but that those PFC regions that are more activated for recall than for recognition tests will tend to occur in the left PFC whereas those PFC regions that are more activated for recognition than for recall will tend to occur in the right PFC. In contrast, the systematic–heuristic hypothesis predicts that the lateralization of PFC should follow the rows of the matrix: the left PFC should be more activated for more systematic (SCR/CRN) than for more heuristic (ACR/IRN) tasks, whereas the right PFC would show the reverse trend. Thus, we were interested in commonalities and differences across pairs of tasks rather than in activations specific to a single task.

A secondary goal of the study was to investigate differences in activation between recall and recognition tasks and between systematic and heuristic tasks beyond the PFC. In a previous PET study in which we compared associative recall and associative recognition (Cabeza, Kapur, et al., 1997), we found the anterior cingulate, the cerebellum, and striatal regions to be more activated for recall than for recognition, whereas the posterior parietal cortex was more activated for recognition than for recall. In the present study, we investigated if these differences would generalize to other forms of recognition and recall. Another interesting issue is the recruitment of medial temporal lobe (MTL) regions during episodic retrieval. Although several PET and fMRI studies have found significant MTL activity during episodic retrieval (for reviews, see Cohen et al., 1999; Schacter et al., 1999; Lepage, Habib, & Tulving, 1998) it is unclear if this activity varies across different forms of episodic retrieval.

RESULTS

Behavioral Results

The proportion of correct recall was 0.75 in ACR and 0.71 in SCR. The proportion of correct recognition in CRN was 0.87, which adjusted for chance [(0.87 − 0.50) × 2] is equivalent to 0.74. In IRN, there were 0.76 hits and 0.07 false alarms, yielding a corrected recognition score of 0.69. In an ANOVA performed on corrected memory performance, the main effect of test was nonsignificant ($F < 1$), suggesting similar levels of episodic recovery in the four tests.

PET Results

Figure 2 and Table 2 show brain regions where activity varied as a function of the production-monitoring factor,

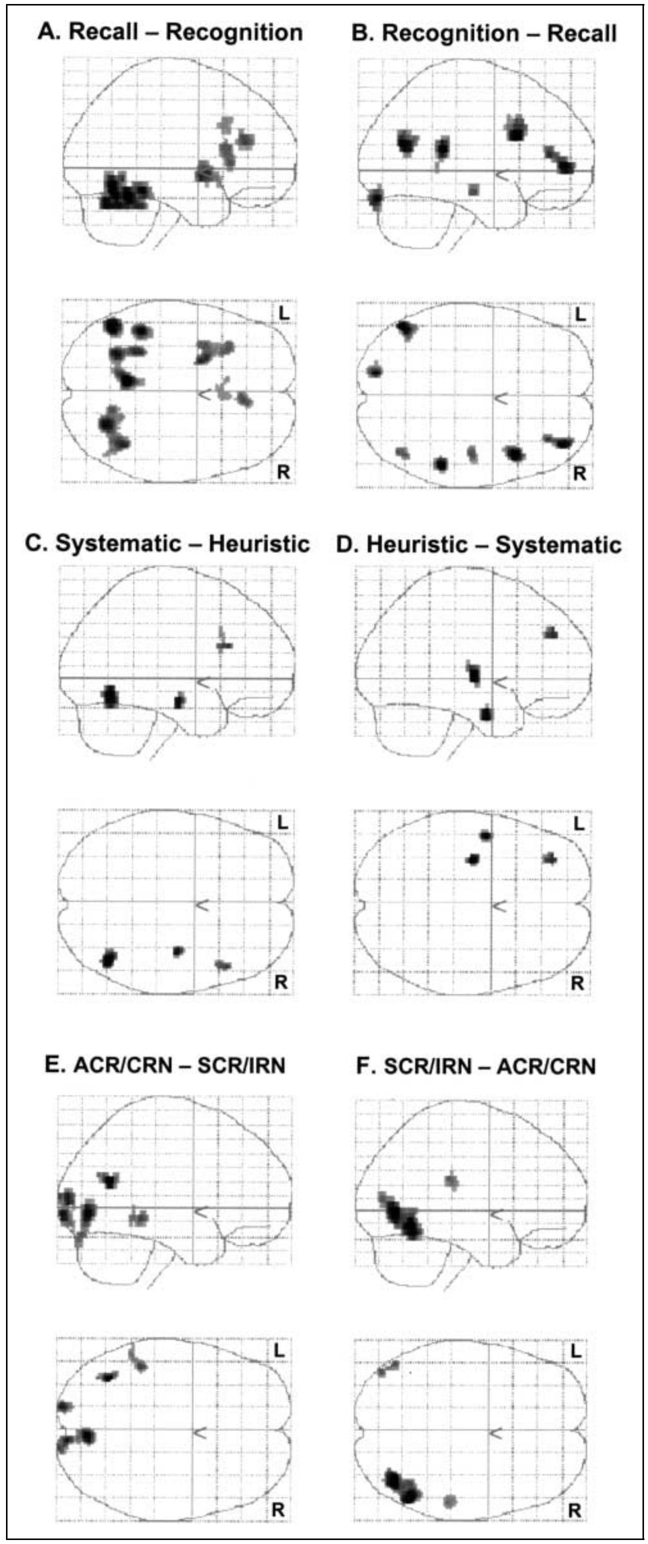

Figure 2. Brain regions showing significant differences in activity as a function of the production-monitoring factor, the systematic–heuristic factor, and their interactions.

Table 2. Brain Regions Showing Differences in Activity as a Function of Production/Monitoring and Systematic–Heuristic Factors and their Interactions

Region	*L/R/M*	*BA*	*x*	*y*	*z*	*Z*
Production/Monitoring						
A. Recall − recognition						
PFC	L	45	−32	24	4	3.7
Anterior cingulate	M	32	6	34	20	3.9
cortex	M	32	4	20	36	3.4
Cerebellum	M		−8	−52	−20	5.2
	L		−26	−58	−28	4.4
	R		26	−62	−28	4.5
Occipito-temporal	L	37/19	−46	−62	−16	5.0
cortex	L	20/37	−44	−42	−16	4.7
Globus pallidus/ putamen	L		−22	2	−4	4.2
B. Recognition − recall						
PFC	R	9/44	44	16	24	4.4
	R	10/46	36	50	4	4.1
Parieto-occipital cortex	L	39/19	−50	−68	20	4.2
	R	39/19	42	−70	24	3.6
Temporal cortex	R	22/42	52	−38	16	4.3
	R	21	44	−14	−16	3.6
Occipital cortex	L	18	16	−86	−20	4.0
Systematic/Heuristic						
C. Systematic − heuristic						
PFC	R	46/44	44	24	24	3.5
Temporo-occipital	R	37/19	44	−62	−12	4.2
MTL	R		36	−12	−16	3.9
D. Heuristic − systematic						
PFC	L	9	−34	44	32	3.6
Temporal pole	L	20/21	−48	−4	−28	3.9
Insula	L		−32	−14	4	4.1
Interactions						
E. ACR/CRN − SCR/IRN						
Temporal cortex	L	21/37	−46	−38	−8	3.6
Parieto-occipital cortex	L	39/19	−38	−62	20	4.4
Occipital cortex	R	18	6	−76	−4	4.1
	R	18/17	8	−92	8	3.9
	L	18	−16	−96	−4	3.9
F. SCR/IRN − ACR/CRN						
Temporo-occipital	R	37/19	50	−58	−12	4.6
Occipital cortex	R	19	38	−70	0	4.5
	L	19	−50	−70	−4	3.6
Anterior parietal	R	40	54	−30	24	3.5

the systematic–heuristic factor, and their interaction. Consistent with the production-monitoring hypothesis, the left PFC was more activated for recall than for recognition (see Figure 2A and Table 2A), whereas the right PFC was more activated for recognition than for recall (see Figure 2B and Table 2B). Left PFC activity associated with production processes was found in the ventrolateral cortex (Brodmann's area [BA] 45), and right PFC activity associated with monitoring processes was found in two distinct loci, one in the dorsolateral cortex (BA 46/44) and one in the anterior cortex (e.g., BA 10). Inconsistent with the systematic–heuristic hypothesis, the right PFC (BA 46/44) was more activated for systematic than for heuristic tasks (see Figure 2C and Table 2C), whereas the left PFC (BA 9) was more activated for heuristic than for systematic tasks (see Figure 2D and Table 2D). To investigate possible interactions between production-monitoring and the systematic–heuristic factors, we performed diagonal contrasts between the cells in the matrix in Figure 1 (i.e., ACR/CRN minus SCR/IRN, and SCR/IRN minus ACR/CRN) but these contrasts did not yield any significant difference in PFC activity (see Figure 2E and F and Table 2E and F). The results of hypothesis-driven SPM contrasts were confirmed with a data-driven partial least squares (PLS) analysis (McIntosh, Bookstein, Haxby, & Grady, 1996).

To further investigate the production-monitoring hypothesis, we also conducted every possible pairwise contrast between recall and recognition tasks. As shown in Figure 3 and Table 3, a hemispheric asymmetry in PFC activity consistent with the production-monitoring hypothesis was found in each one of these contrasts. Each pairwise recall minus recognition subtraction yielded activations in the left PFC (see Figure 3A), whereas each pairwise recognition minus recall subtraction yielded activations in the right PFC (see Figure 3B). The exact location of the activations varied, but these differences may be due to the small differences among the encoding conditions of the individual tasks, and therefore should be interpreted with caution. More important is the fact that the lateralization pattern was always the same: Recall was associated with left PFC activity, and recognition with right PFC activity.

Beyond PFC, significant differences were found as an effect of both factors and their interactions. Table 2A and B shows regions that were differentially recruited by recall and recognition tasks. Compared to recognition tasks, recall tasks were associated with activations in cingulate, cerebellar, left occipitotemporal, and left striatal (putamen/globus pallidus) regions (see Table 2A). Compared to recall tasks, recognition tasks were associated with bilateral parietal and right temporal regions (see Table 2B). The systematic–heuristic factor and its interaction with the production-monitoring factor yielded several small activations in posterior brain regions (see Figure 2C to F). The most interesting of these activations occurred in a right MTL region in the vicinity of the right hippocampus (see Table 2C) that was more activated for systematic than for heuristic tasks.

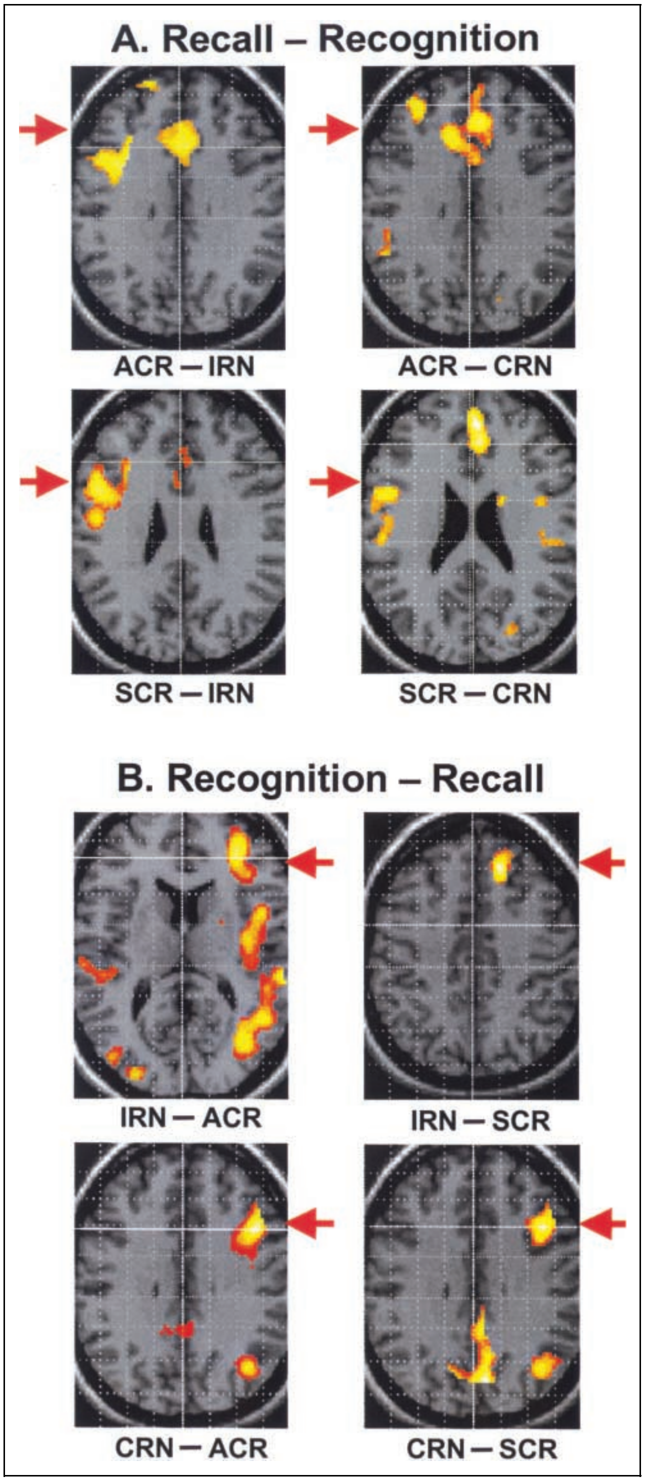

Figure 3. PFC regions showing significant activation differences in pairwise comparisons between recall and recognition tasks.

DISCUSSION

In sum, the lateralization of PFC activity across tasks was consistent with the production-monitoring hypothesis but not with the systematic–heuristic hypothesis. The study also yielded several interesting activations outside the PFC. These two sets of findings are discussed in the following sections.

Lateralization of PFC Activity

The finding that the left PFC was more activated for recall than for recognition tasks whereas the right PFC was more activated for recognition than for recall tasks (see Table 3 and Figure 3) supports the production-monitoring hypothesis (Assumption 1). These results fit very well the idea that the left PFC is more involved in semantically guided information production procedures, whereas the right PFC is more involved in monitoring operations, including the evaluation and verification of recovered information. The results are also consistent with the idea that the left hemisphere makes inferences and generalizations that go beyond available information, whereas the right hemisphere is less capable of inferences and generalizations, and, hence, more veridical (Metcalfe, Funnell, & Gazzaniga, 1995). Consistent with this idea, studies with split-brain patients have shown that the left hemisphere tends to accept lures related to studied scenes, words, faces, and visual patterns, whereas the right hemisphere tends to reject them (Metcalfe et al., 1995; Phelps & Gazzaniga, 1992). According to the production-monitoring hypothesis, this effect would be a clear example of what happens when semantically guided production processes mediated by the left PFC are not checked by monitoring and verification processes mediated by the right PFC. Whereas research with split brain cannot determine whether

Table 3. PFC Regions Showing Significant Activation Differences in Pairwise Comparisons Between Recall and Recognition Tasks

Region	*L/R*	*BA*	*x*	*y*	*z*	*Z*
A. Recall – recognition						
ACR – IRN	L	45/46	−50	26	12	3.9
ACR – CRN	L	9	−30	44	36	3.8
SCR – IRN	L	45/46	−50	24	12	4.3
SCR – CRN	L	44/6	−44	0	32	3.3
B. Recognition – recall						
IRN – ACR	R	9/44	46	14	24	4.2
	R	46/10	32	40	12	4.0
IRN – SCR	R	8/9	16	36	40	3.7
CRN – ACR	R	9/44	44	16	24	5.2
	R	46/10	32	38	12	4.1
	R	10/46	36	50	4	3.4
CRN – SCR	R	9	44	20	36	4.1

these differences reflect the function of anterior or posterior brain regions, or whether they occur during encoding or during retrieval, the present results suggest they are related to the role of the left and the right PFC during the retrieval phase of episodic memory.

The current results are also consistent with idea that the amount of production and monitoring operations varies among different recognition tasks (Assumption 2). As noted in the Introduction, context-recognition tasks are likely to involve greater production and monitoring components than simple item recognition (Nolde et al., 1998; Johnson et al., 1993). In most functional neuroimaging studies that directly compared context and item recognition, context recognition was associated with bilateral PFC activations (Raye, Johnson, Mitchell, & Nolde, 2000; Henson, Shallice, et al., 1999; Rugg, Fletcher, Chua, & Dolan, 1999; Cabeza, Mangels, et al., 1997). The production-monitoring hypothesis suggests that left PFC activations during context retrieval may reflect production processes, and right PFC activations, monitoring processes. To investigate this idea, we compared context to item recognition (CRN–IRN). This contrast identified brain regions that were more activated during context than during item retrieval, but it could also have been affected by minor encoding differences between the two tests. As illustrated by Figure 4B, the CRN–IRN contrast yielded two significant PFC activations, one in the left ventrolateral PFC (BA 47) and one in the right dorsolateral PFC (BA 9). Consistent with the production-monitoring hypothesis, the left PFC region was also activated by the two recall tasks (see Figure 4A), whereas the right PFC region was not (see Figure 4C).

The present results suggest that context memory has an important production component mediated by the left PFC, which is subtracted out when the control task is a recall test (see Table 3B and Figure 3B) but is evident when the control task is an item-recognition test (Figure 4B).

The current data are also consistent with the notion that production and monitoring processes can be further subdivided within the left and right PFC, respectively (Assumption 3). Functional neuroimaging evidence suggests that within the left PFC, semantic processes tend to engage primarily ventrolateral regions, verbal/phonological processes, opercular regions, and manipulation processes, dorsolateral regions (e.g., Poldrack et al., 1999; Kapur et al., 1996; Owen et al., 1996). The location of production-related left PFC activations in Table 3A are consistent with these distinctions: A ventrolateral area (BA 45) was activated by both SCR and ACR, which involved semantic processing; an opercular area (BA 44) was recruited mainly by SCR, which involved the generation of words that fitted an orthographic/phonemic word stem; and a dorsolateral area (BA 9) was engaged mainly by ACR, which involved strategic retrieval of semantic associations established during encoding. As for monitoring operations in the right PFC, whereas some right PFC regions were associated with both CRN and IRN (e.g., BAs 9/44 and 46/10 in Table 3B), the more dorsal right PFC region depicted in Figure 4B was associated with CRN but not with IRN. Thus, some right PFC areas may reflect generic monitoring operations, whereas others may reflect monitoring operations more specific to context retrieval. It is worth noting that a right frontopolar region was more activated for CRN than for ACR, possibly reflecting greater monitoring demands for source memory than for recall. In experiments in which episodic retrieval is compared to non-episodic retrieval conditions, frontopolar activations may reflect the mental set of episodic retrieval or retrieval mode (Cabeza, Dolcos, Graham, & Nyberg, 2002; Düzel et al., 1999; Cabeza, Kapur, et al., 1997; Nyberg et al., 1995). In the present study, however, retrieval mode was constant across the conditions, and, hence, the findings are orthogonal to the concept of retrieval mode. The finding of a frontopolar activation when retrieval mode was constant is not inconsistent with the notion of retrieval mode, because it is perfectly possible for a brain region to be involved in retrieval mode and at the same time to be modulated by monitoring demands.

Tentative support was also found for the idea that the production-monitoring asymmetry of PFC activation is independent from the level of memory recovery (Assumption 4). In the current study, performance did not differ significantly across the four tasks, yet the expected pattern of greater left PFC activity during production operations and greater right PFC activity during monitoring operations held. The asymmetry of PFC asymmetry seems also independent of the level of

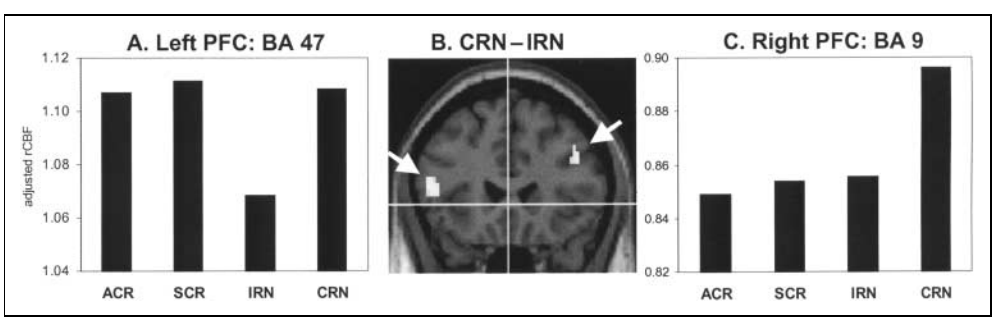

Figure 4. The CRN–IRN contrast yielded two significant activations in PFC regions, one in the left PFC (BA 47; *xyz*: −50 26 12; *Z* score: 3.9) and one in the right PFC (BA 9; *xyz*: 46 18 36; *Z* score: 3.9). Adjusted rCBF in these two regions is plotted for ACR, SCR, IRN, and CRN tasks.

recollection versus familiarity because IRN and CRN were associated with the same lateralization pattern. Future studies will test whether this assumption holds when differences in memory recovery levels exist across tasks. The current study was not designed to investigate the idea that production processes precede monitoring processes (Assumption 5). This idea will be investigated using ERPs.

Although the present results are more consistent with the production-monitoring hypothesis than with the systematic–heuristic hypothesis, the two hypotheses are not completely incompatible. Johnson and Raye (2000) and Nolde et al. (1998) argued that generation of retrieval cues is a systematic process, and, as such, both hypotheses predict left PFC activity during production processes. Furthermore, Johnson and Raye state that familiarity-based decisions that often occur in old–new recognition tasks are heuristically based. Both hypotheses therefore predict right PFC activity during such familiarity-based recognition judgments. However, the systematic–heuristic hypothesis cannot easily account for several of the present results. For example, why were there differences in PFC lateralization when behavioral results suggest that difficulty was equivalent across all tasks? The systematic–heuristic hypothesis assumes that when a retrieval task is difficult or accuracy is important, systematic processes are engaged in order to monitor and evaluate the retrieved information (Johnson & Raye, 2000). Yet, in the current study, we observed striking differences in the PFC lateralization, despite similar levels of accuracy across tasks. Thus, although the systematic–heuristic distinction is a very useful distinction for memory research (Johnson et al., 1993; Johnson & Raye, 2000), the present results suggest that the production-monitoring distinction provides a more complete and parsimonious account of the lateralization of PFC activity during episodic retrieval.

Activations Outside the PFC

There were two interesting sets of findings outside the PFC. First, several regions showed significant differences in activation between recall and recognition tests. Anterior cingulate, cerebellar, and striatal (globus pallidus/putamen) regions were more activated for recall than for recognition, whereas parietal regions were more activated for recognition than for recall. These activations replicate almost exactly the results of our previous recall–recognition PET study (Cabeza, Kapur, et al., 1997). Because the particular recall and recognition tasks employed in the two studies were different, the convergence of results strongly suggests that these activation patterns reflect fundamental differences between the neural correlates of recall and recognition. The interpretations we proposed in our previous study (Cabeza, Kapur, et al., 1997) also seem to apply to the present results. We attributed anterior cingulate and cerebellar activations during recall to initiation of action (for a review, see Devinsky, Morrell, & Vogt, 1995) and self-initiated retrieval processes (Bäckman et al., 1997), respectively, and both ideas fit well with the role of the left PFC in production processes. In our previous study, we proposed that parietal activity during recognition could reflect a greater perceptual component of recognition tasks (Cabeza, Kapur, et al., 1997). This idea harmonizes with the notion of monitoring because the evaluation of perceptual information is an important aspect of verification processes (e.g., Johnson et al., 1993).

A second interesting finding outside the PFC was a right MTL region that was more activated for systematic (SCR and CRN) than for heuristic (ACR and IRN) tasks. Whereas previous functional neuroimaging studies of episodic retrieval have typically found differences in MTL activity as a function of the amount (e.g., Eldridge, Knowlton, Furmanski, Bookheimer, & Engle, 2000; Rugg, Fletcher, Frith, Frackowiak, & Dolan, 1997; Nyberg, McIntosh, Houle, Nilson, & Tulving, 1996; Schacter, Alpert, et al., 1996) or type (e.g., Cabeza et al., 2001) of episodic information recovered, the present study yielded a difference in MTL activity as a function of the kind of episodic retrieval task employed. Although it is unclear what cognitive process underlies the right hippocampal activation, one candidate process is the integration of perceptual aspects of retrieved information and retrieval cues. Perceptual integration is important for CRN because decisions in this task depend on the match/mismatch between the sensory properties of studied words (visual vs. auditory) and test words. Perceptual integration is also important for SCR because the words generated in this task must match the orthographic structure of the word-stem cues. Conversely, perceptual integration seems less important for IRN, in which modality was constant and stimuli were not degraded, and for ACR, in which modality was constant and the target was a perceptually independent unit. Although the notion of perceptual integration seems to accommodate the present hippocampal activation, this idea is very speculative and may not fit with other ideas regarding hippocampal function.

Conclusions

We proposed and tested the hypothesis that the left PFC is differentially more involved in production processes than is the right PFC, whereas the right PFC is differentially more involved in monitoring processes than is the left PFC. Consistent with this production-monitoring hypothesis, left PFC regions were more activated during recall than during recognition tasks, and right PFC regions were more activated during recognition than during recall. At present, the production-monitoring hypothesis is limited to the verbal episodic retrieval domain. Ranganath, Johnson, and D'Esposito (2000) found left PFC activation in a more anterior location to that found here ($y = 49$ vs. $y = 24$ in the current results) during context retrieval of picture size. As stated in the Introduction, we assume that there are different kinds of production processes (and different kinds of monitoring processes), that may correspond to different functional regions within the left (and right) PFC. Hence, Ranganath et al.'s finding may reflect a more perceptually guided production process than the left PFC described in the current study. Future research will reveal help to refine the production/monitoring hypothesis so that it captures more general aspects of the function of the left and right PFC and eventually may be extended to other cognitive domains.

METHODS

Subjects

Twelve subjects (7 female, 5 male) between the ages of 20 and 35 years (mean: 25.3 years) participated in the study. They were all right-handed, had no history of neurological or psychiatric illness, and were not taking any medication known to affect blood flow. The study was approved by the joint Baycrest Centre/University of Toronto Research Ethics and Scientific Review Committee.

Behavioral Methods

Before each scan, subjects studied a list of 24 target words (SCR, IRN, and CRN conditions) or word pairs (ACR condition) plus one primacy and two recency fillers. In the CRN condition, 12 targets were presented auditorily and 12 targets were presented visually, in that order. In all conditions, the study list was presented once before one scan or four times before another scan, but for the present analyses we averaged across this manipulation. The presentation rate at study was 3 sec/item, except in the IRN condition, in which it was 750 msec/item, to equate accuracy in the IRN task with performance in the other three tasks. During each scan, subjects performed one of the four tasks. The IRN test list consisted of 14 studied words (all during the 60-sec scan window) plus 10 nonstudied lures (4 before, 2 during, and 4 after the scan window). The SCR test list consisted of the three-letter stems of the 24 targets. The ACR test consisted of the first word of each of the 24 pairs. The CRN test list consisted of 24 visually presented words (12 studied visually, and 12 studied auditorily). At test, words were presented for 4 sec followed by fixation for 1 sec. The test list started 30 sec before and continued 30 sec after the 60-sec scan window. In all conditions, subjects responded to each item by saying one word aloud: "old" or "new" in IRN task; the word recalled in ACR and SCR; and "seen" or "heard" in CRN. In the SCR and ACR trials, if subjects could not recall a word before fixation appeared, they said "pass," so that one word was spoken in every trial.

PET Methods

Two PET scans were conducted for each of the four tasks, with repeated scans forming a mirror image (ABCD–DCBA) and the order of four tasks counterbalanced across subjects. PET scans were obtained with a GEMS-Scanditronix PC2048-15B head scanner using a bolus injection of 35.5 mCi of ^{15}O-labeled H_2O. Image processing and statistical analyses were performed using SPM99b (Wellcome Department of Cognitive Neurology, London, UK) implemented in Matlab (Mathworks, Sherborn, MA). First, the different images from each subject were realigned to the first image. Second, the realigned images from each subject were transformed into a standard space (using the MNI template provided by SPM99b) and smoothed using a 10-mm isotropic Gaussian kernel. Third, the effects of the conditions on the regional cerebral blood flow at each voxel were estimated using a general linear model, wherein the changes in global counts are considered as a covariate. The statistical contrasts followed the 2×2 design, and investigated (1) the production-monitoring factor (i.e., recall minus recognition, and recognition minus recall), (2) the systematic–heuristic factor (i.e., systematic minus heuristic, and heuristic minus systematic), and (3) the interaction between the two factors (i.e., ACR/CRN minus SCR/IRN, and SCR/IRN minus ACR/CRN). The effects of each comparison were estimated using linear contrasts, which yield a t statistic (expressed as a Z score) for a given comparison at each voxel. The significance threshold was set to the standard $Z > 3.09$ ($p < .001$ uncorrected). To further reduce the risk of false positive activations, activations including less than 20 contiguous voxels were not considered.

Acknowledgments

This research was supported by grants from AHFMR (Alberta, Canada) and NSERC (Canada) to R. C. We thank Dan Dillon, Marcia Johnson, Kevin LaBar, Lars Nyberg, David Rubin, Jennifer Talarico, and Endel Tulving for insightful comments on earlier versions of this article, and Roger Lennartsson and Randy McIntosh for technical support.

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