

# Wada Testing Reveals Frontal Lateralization for the Memorization of Words and Faces

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## Abstract

■ Neuroimaging studies have suggested that specific regions of the frontal and medial temporal cortex are engaged during memory formation. Further, there is specialization across these regions such that verbal materials appear to preferentially engage the left regions while nonverbal materials primarily engage the right regions. An open question, however, has been to what extent frontal regions contribute to successful memory formation. The present study investigates this question using a reversible lesion technique known as the Wada test. Patients memorized words and unfamiliar faces while portions of their left and right

hemispheres were temporarily anesthetized with sodium amytal. Subsequent memory tests revealed that faces were remembered better than words following left-hemisphere anesthesia, whereas words were remembered better than faces following right-hemisphere anesthesia. Importantly, inspection of the circulation affected by the amytal further suggests that these memory impairments did not result from direct anesthetization of the medial temporal regions. Taken in the context of the imaging findings, these results suggest that frontal regions may also contribute to memory formation in normal performance. ■

## INTRODUCTION

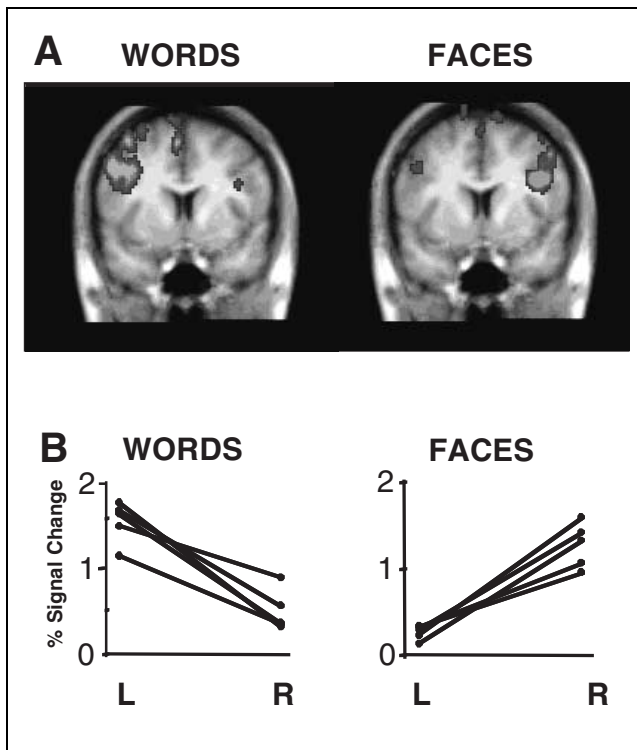
Over the past four decades, neuropsychological and nonhuman primate studies have highlighted the importance of medial temporal lobe structures to memory formation (Schacter & Tulving, 1994; Cohen & Eichenbaum, 1993; Squire, 1992). Less focus has been directed to results that implicate the frontal lobes in at least some aspects of memory performance. More recently, neuroimaging studies have refocused interest on frontal contributions to memory. The neuroimaging data suggest that specific areas of the frontal cortex are engaged across a wide range of tasks that encourage memory formation (Brewer, Zhao, Desmond, Glover, & Gabrieli, 1998; Kelley et al., 1998; Wagner, Poldrack, et al., 1998; Wagner, Schacter, et al., 1998; Dolan & Fletcher, 1997; Haxby et al., 1996; Kapur et al., 1994, 1996; Demb et al., 1995). Moreover, the laterality of these activations is strongly influenced by the materials being memorized (Figure 1). Memorization of verbal materials (e.g., words) more strongly activates frontal regions of the left hemisphere (McDermott, Buckner, Petersen, Kelley, & Sanders, 1999; Kelley et al., 1998; Wagner, Poldrack, et al., 1998; Wagner, Schacter, et al., 1998; Dolan & Fletcher, 1997; Kapur et al., 1994, 1996; Demb et al., 1995), whereas memorization of nonverbal materials

(e.g., unfamiliar faces or textures) more strongly activates homologous frontal regions of the right hemisphere (McDermott et al., 1999; Brewer et al., 1998; Kelley et al., 1998; Wagner, Poldrack, et al., 1998).

Neuroimaging studies have also noted medial temporal activations during tasks that encourage memory formation. In some instances, laterality effects similar to those observed in the frontal cortex were observed (Brewer et al., 1998; Kelley et al., 1998; Wagner, Schacter, et al., 1998). Furthermore, a recent meta-analysis of imaging studies of episodic memory formation showed that the majority of these medial temporal activations were localized to more posterior regions of the medial temporal lobe (Schacter & Wagner, 1999). These medial temporal activations converge nicely with the neuropsychological data, and together make a very compelling argument that medial temporal lobe activity is critical to memory formation.

But is frontal participation critical to successful memory formation? While imaging studies suggest that the left and right frontal regions contribute differentially to the performance of memorization tasks, they do not demonstrate definitively that frontal participation is critical for memory formation to occur. The hemispheric asymmetries observed in these studies do however make strong (and testable) predictions regarding the importance of frontal activity to memory formation. If the participation of the frontal cortex is also necessary

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**Figure 1.** Hemispheric asymmetries in the frontal cortex during intentional memorization tasks. (A) Coronal sections show fMRI activity in the dorsal frontal cortex during intentional memorization of words and unfamiliar faces. Memorization of words activates the left frontal cortex, whereas memorization of unfamiliar faces activates the right frontal cortex. The data (Kelley et al., 1998) are averaged across five subjects and are displayed in Talairach and Tournoux (1988) atlas space. The left side of the images correspond to the left side of the brain. (B) Percent signal change in left (L) and right (R) dorsal frontal cortex for each subject. Each line corresponds to the left and right signal intensities from one subject. Signal intensities were calculated by comparing each memorization task to a baseline control task in which subjects fixated on a crosshair.

for memory formation, then lack of participation of the left frontal cortex will selectively disrupt memory formation for verbal materials and lack of participation of the right frontal cortex will selectively disrupt memory formation for nonverbal materials.

Alternatively, it may be the case that episodic memory formation relies exclusively on medial temporal regions. It is well established that circumscribed bilateral lesions to medial temporal lobe structures often result in a severe and pervasive inability to remember new experiences. If memory formation depends only on these regions, then the frontal activations observed using fMRI may be epiphenomenal to successful memory formation, and disruption of this activity during a memorization task should not result in marked memory impairment.

One way to distinguish between these two hypotheses would be to conduct a lesion study in which specific frontal regions were damaged while leaving other areas known to be important to memory formation relatively intact (e.g., the medial temporal lobe). Unfortunately,

lesions are typically permanent and, as a result, would not allow for successive testing of left- and right-hemisphere frontal regions in the same patient. To further complicate matters, permanent lesion studies often cannot readily dissociate memory formation from other memory processes such as memory retrieval. Put differently, when a patient with a permanent lesion fails on a memory test, it is unknown to what extent the failure is due to an impairment of the formation of a memory trace or its retrieval. If a lesion was reversible, however, the procedure could be performed separately on both left- and right-hemisphere regions. Additionally, reversible lesions may allow the added advantage of capturing the isolated contributions of specific mnemonic stages. For example, a reversible lesion could be induced during a memorization task to selectively disrupt memory formation and then later “reversed” to permit normal attempts at memory retrieval.

The present study investigates this possibility in 21 patients undergoing a preoperative neuropsychological procedure known as the intracarotid sodium amobarbital, or Wada, test (Wada, 1949; Wada & Rasmussen, 1960). The Wada test is essentially a reversible lesion study used to predict postoperative speech and memory functions (Milner & Taylor, 1972) in patients that are candidates for neurosurgery. The particular psychological tasks employed during the test can vary across institutions. In the version of the Wada test employed here, sodium amytal is injected into the internal carotid artery (ICA) to selectively and temporarily anesthetize a portion of one hemisphere (including the frontal regions describe above). During this period of anesthesia, language abilities are assessed and a memorization task, consisting of four to-be-remembered words and four unfamiliar faces, is administered. Once the patient recovers from the effects of the amytal, a recognition memory test is given. The procedure is then repeated in the opposite hemisphere. Based on the findings from functional neuroimaging studies, we expected that anesthetization of left-hemisphere regions would impair memory formation for verbal materials (words), whereas anesthetization of right-hemisphere regions would impair memory formation for nonverbal materials (unfamiliar faces).

## RESULTS

The procedure was performed successfully in all 21 patients. A brief synopsis of each patient is presented in Table 1.

### Language Assessment

Of the 21 patients tested, 18 were determined to be left-hemisphere dominant for language (15 were right-handed, 3 were left-handed) and 3 were found to be right-hemisphere dominant for language (patients P2, P7, and P16). This report only focuses on the memory

**Table 1.** Summary of Patient Histories

<i>Patient</i>	<i>Age</i>	<i>Sex</i>	<i>Handedness</i>	<i>Etiology/ Type of Seizures</i>	<i>Probable Location</i>	<i>Frequency of Seizures (per month)</i>	<i>Age of Onset (years)</i>	<i>Recent Medications</i>
P1	35	M	R	Oligodendroglioma	Right temporal	N/A	N/A	N/A
P2	41	M	R	CPS	Left temporal	2–3	22	Te, La
P3	27	M	R	CPS	Left temporal	4	1	La, My
P4	43	F	L	Astrocytoma	Right temporal	N/A	N/A	N/A
P5	47	F	R	Granulomatous mass	Right temporal	N/A	N/A	N/A
P6	37	F	L	Astrocytoma	Right temporal	N/A	N/A	N/A
P7	28	M	L	CPS	Left temporal	1–2	8	De, G
P8	19	M	R	CPS	Right temporal	6–8	1	La, G, Ca, Lo
P9	25	F	R	CPS	Bilateral temporal	10	4	G, Ca
P10	30	F	R	CPS, cystic lesion	Left temporal	7	1	Te, La, P, Cl
P11	47	M	R	CPS, GTCS	Unknown	6–10	36	To, Di, N
P12	39	F	R	CPS	Left temporal	8–10	29	G
P13	33	M	R	SPS	Right motor	1	16	Di, F, Te
P14	19	M	R	Neoplasm	Left temporal	N/A	N/A	N/A
P15	20	M	R	CPS	Left temporal	2	<1	N, Di
P16	44	F	L	AVM	Right frontal	N/A	N/A	N/A
P17	49	F	R	CPS, GTCS	Right temporal	10	2	Di, P, Ls
P18	35	F	R	CPS	Left temporal	3	1	Te, N
P19	40	F	R	CPS	Left temporal	1–3	32	Te, N, La, P
P20	45	F	R	SPS, GTCS	Right temporal	2–10	4	To
P21	35	F	R	CPS	Right temporal	2–3	8	Te

Abbreviations: M = male; F = female; R = right; L = left; CPS = complex partial seizures; GTCS = generalized tonic-clonic seizures; SPS = simple partial seizures; AVM = arterio-venous malformation; Te = tegretol; La = lamictal; Ls = lasix; My = mysoline; De = depakote; G = gabatril; Ca = carbamazepine; Lo = lorazepam; P = phenobarbital; Cl = clorazepate; To = topamax; Di = dilantin; N = neurotonin; F = felbatol.

results of the 18 patients that were left-hemisphere dominant for language. This is because (1) the imaging studies that report laterality differences in the frontal cortex examined subjects that were strongly right-handed and presumably left-hemisphere dominant for language, and (2) there were too few right-hemisphere language dominant patients to perform adequate statistical analyses.

### Angiography Results

The Wada procedure has become the “gold standard” for evaluating language function. However, its ability to predict memory function following unilateral medial temporal lobe resection has been highly variable (Loring, Meador, Lee, Martin, & Huh, 1998; Jack, Nichols, Sharbrough, Marsh, & Petersen, 1988; Jack et al., 1989). This may be related, in part, to the inconsistent delivery of sodium amytal to medial temporal lobe structures during Wada testing. The anterior cerebral arteries

(ACAs), which supply the parasagittal frontal and parietal lobes, and the middle cerebral arteries (MCAs), which supply the lateral frontal, parietal, and temporal lobes, are branches of the ICA. Blood flow to the frontal regions activated in fMRI studies of memory formation is nearly completely supplied by the MCA.

By contrast, most of the medial temporal lobes, particularly the posterior portion, is traditionally thought to be supplied by the posterior cerebral arteries (PCAs), which ordinarily receive the most flow from the vertebrobasilar system and not the ICA (Margolis, Newton, & Hoyt, 1974; Stephens & Stiwel, 1969; Muller & Shaw, 1965). The ICA can supply some circulation to the anterior temporal lobe regions via the cisternal segment of the anterior choroidal artery, but this supply is typically limited to portions of the amygdala, uncus, and perhaps a small portion of the anterior hippocampus (Margolis et al., 1974; Carpenter, Noback, & Moss, 1954). The medial temporal activations observed in the Kelley et al. (1998) study and many other fMRI studies of

memory formation were located in the more posterior region of the medial temporal lobe (for review see Schacter & Wagner, 1999)—the portion that falls “outside” the normal distribution of the ICA.

Thus, an open question was whether injection of amytal into the internal carotid circulation using the current methods would generally perfuse the posterior medial temporal lobe regions shown to be active during imaging studies of memory formation. To help address this question in the current group of patients, digital subtraction angiography images of the left (LICA) and right (RICA) internal carotid circulation were examined independently by two neuroradiologists to determine the extent of PCA filling. For each image, PCA filling was rated as (1) complete, (2) moderate, (3) minimal, or (4) absent relative to MCA filling. Of the 36 hemispheres evaluated, the two neuroradiologists were in complete agreement on 33 hemispheres. For the 3 hemispheres (all left) in which there was disagreement, the ratings differed by only one category point (moderate vs. minimal in all three instances).

Inspection of the angiography images revealed that PCA filling following RICA angiography was complete in only two patients (P11 and P18). In these two patients, there was a very large posterior communicating (PCOM) artery, or a direct “fetal” type origin of the PCA from the ICA (this variation occurs in about 10% of the adult population). For these patients, the catheter was advanced further in the ICA to minimize administration of amytal to the PCA. Of the remaining 16 patients, PCA filling was rated as moderate in a third patient, but was minimal (6) or absent (9) in the remaining 15 patients. Figure 2 shows examples of complete versus absent PCA filling following RICA angiography in two patients. PCA filling following LICA angiography was rated as moderate or minimal in three patients. These were the three hemispheres for which ratings differed. One neuroradiologist rated PCA filling as moderate for these three patients; the second neuroradiologist rated PCA filling as minimal in these patients. For the remaining 15 patients, PCA filling was rated as minimal in 6 patients and absent in the 9 remaining patients. These results are summarized in Table 2.

Thus, for the vast majority of these patients, PCA filling was minimal or absent. This suggests that amytal was very rarely delivered to the posterior medial temporal regions shown to be active in previous neuroimaging studies. By contrast, angiography images revealed robust MCA filling for each subject, predicting successful delivery of amytal to the ipsilateral frontal regions in all 18 patients.

### Subsequent Memory Performance

Accurate performance on a yes/no recognition memory tests was used as an indication that successful memo-

rization occurred. During the recognition memory test, patients were shown eight words and eight faces; half of these words and faces were “old” items that the patients had studied during the memorization task. Recognition memory performance was determined by calculating corrected recognition scores (HITS – FALSE ALARMS). Thus, a perfect score would be 4, and chance performance would be 0. Results of the BASELINE, LICA, and RICA recognition memory tests are shown in Figure 3. An analysis of variance (ANOVA) examining effects of hemisphere injected (BASELINE/LICA/RICA) and material type (words/faces) revealed a significant hemisphere by material interaction [ $F(1,17) = 39.91, p < .0001$ ], and a significant main effect of hemisphere [ $F(1,17) = 44.14, p < .0001$ ]. Post hoc statistical tests revealed that this main effect was carried largely by the BASELINE condition. BASELINE memory performance was significantly greater than both LICA [ $F(1,17) = 68.96, p < .0001$ ] and RICA [ $F(1,17) = 63.33, p < .0001$ ] performance. There was no significant difference between LICA and RICA memory performance ( $F < 1$ ). The main effect of material type was not significant ( $F < 1$ ).

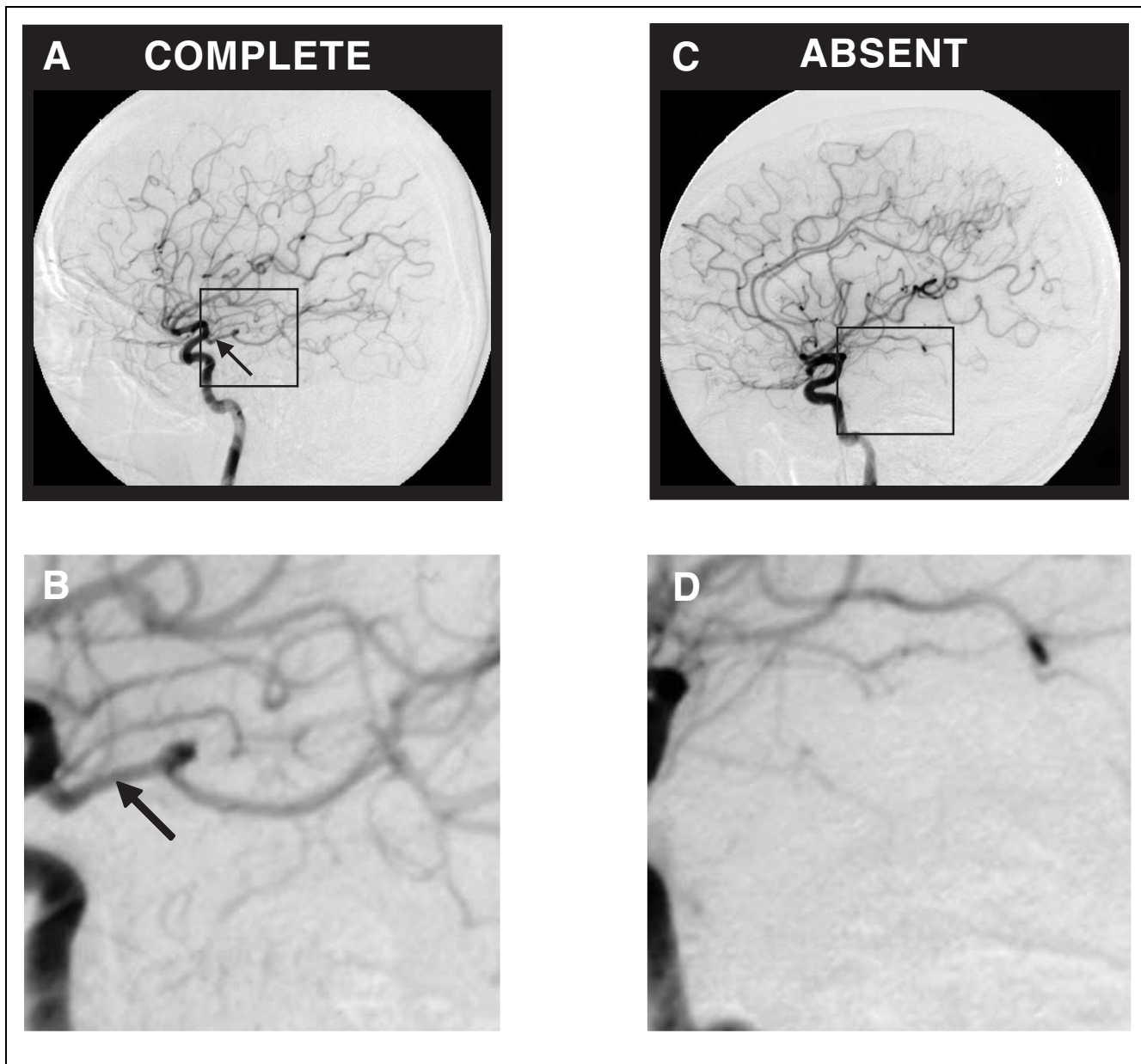
Post hoc statistical tests further revealed significant differences in performance following left- and right-hemisphere anesthesia for each material type. For words, recognition memory performance was significantly greater following the RICA injection than LICA injection [ $F(1,17) = 44.04, p < .0001$ ]. The reverse pattern was true for face recognition; recognition memory performance for faces was significantly better following LICA injection than RICA injection [ $F(1,17) = 35.93, p < .0001$ ]. There were also significant differences between material types within each hemisphere. Recognition memory performance was significantly better for words than faces following RICA injection [ $F(1,17) = 44.03, p < .0001$ ]. By contrast, faces were remembered better than words following the LICA injection [ $F(1,17) = 35.93, p < .0001$ ]. Memory performance for words and faces during the BASELINE condition did not differ ( $F < 1$ ).

In addition, it is interesting to note that BASELINE recognition for faces was significantly better than recognition following LICA injection [ $F(1,17) = 22.18, p < .0001$ ]. Likewise, BASELINE recognition for words was significantly better than recognition following RICA injection [ $F(1,17) = 16.54, p < .0005$ ].

Finally, this same pattern was observed for both left- and right-temporal lobe patients.

### Can Parietal Anesthetization Account for These Hemispheric Memory Differences?

While it is unlikely that direct anesthetization of medial temporal regions found to be active in imaging studies of encoding occurred in most of the patients tested here, the vascular distribution of amytal was not exclusively limited to frontal regions. As mentioned previ-



**Figure 2.** PCA filling following injection of contrast medium into the ICA. Images are sagittal views with the front of the brain facing left. (A) Digital subtraction angiography revealed a direct “fetal” type origin of the right PCA from the right ICA (arrow) or a large PCOM artery in patient P11. This was one of two patients that exhibited complete PCA filling following injection of contrast medium into the right ICA. (B) Enlarged view of the highlighted section in (A). (C) For most of the individuals tested, angiography revealed either minimal or no PCA filling following injection of contrast medium into the ICA. Shown here is an example (patient P8) where PCA filling is absent following right ICA angiography. (D) Enlarged view of the highlighted section in (C).

ously, the ICA supplies arterial circulation to the frontal and parietal regions via the MCA. Thus, a second alternative possibility is that the memory impairments observed here may have resulted from parietal and not frontal or medial temporal anesthetization. To address this possibility, we reexamined our previous functional neuroimaging data (Kelley et al., 1998) to determine whether similar material-specific asymmetries could be detected in the parietal cortex.

Figure 4 shows signal intensities in the left and right parietal regions during intentional memorization of

words and unfamiliar faces averaged across five subjects. Regions of interest for statistical analyses were defined in an unbiased manner. Left and right parietal activations were identified in each subject by comparing a third (independent) memorization task (memorization of namable objects) to a baseline fixation control task (Kelley et al., 1998). The object memorization task was chosen because it yielded robust bilateral parietal activation in this previous study. Magnitudes were then calculated separately for the word and face memorization tasks for the left and right parietal regions in each

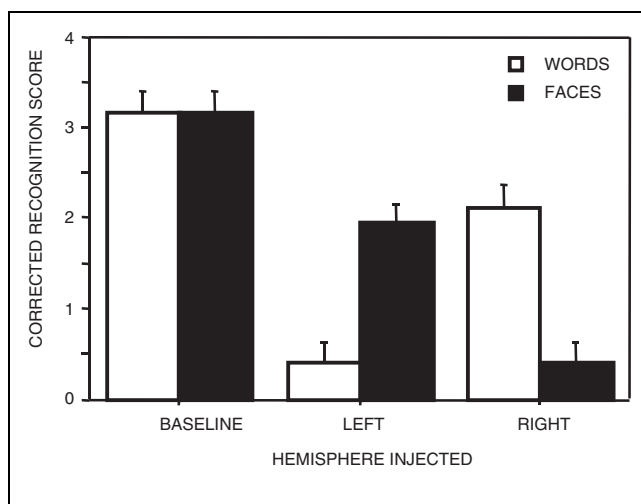
**Table 2.** PCA Filling Following Intracarotid Angiography

	Ratings			
	Complete	Moderate	Minimal	Absent
<i>Neuroradiologist 1</i>				
LICA	0	3	6	9
RICA	2	1	6	9
<i>Neuroradiologist 2</i>				
LICA	0	0	9	9
RICA	2	1	6	9
<i>Totals (expressed as percentage of patients)</i>				
LICA (%)	0	0–17	33–50	50
RICA (%)	11	6	33	50

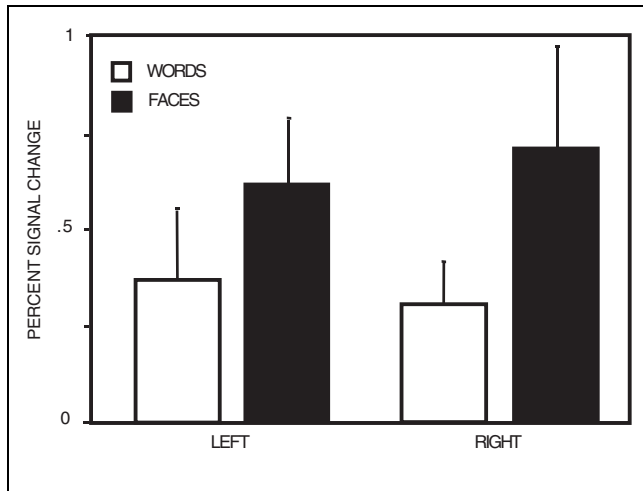
subject. An ANOVA examining the effects of stimulus material (word/face), hemisphere (left/right), and the material-by-hemisphere interaction term revealed no main effects of stimulus material [ $F(2,8) = 2.28, p > .20$ ] and hemisphere ( $F < 1$ ), and no significant interaction ( $F < 1$ ). In other words, hemispheric asymmetries were not observed in the parietal cortex during memorization of words or faces.

## DISCUSSION

The results presented here are consistent with the laterality predictions driven by recent neuroimaging studies. Faces were remembered better than words following left-hemisphere anesthesia. The reverse pat-



**Figure 3.** Subsequent memory for words and unfamiliar faces during BASELINE and following administration of amyntal to the LICA and RICA. Bars indicate standard error of the mean (SEM).



**Figure 4.** Percent signal change in left (L) and right (R) parietal cortex during intentional memorization of words and unfamiliar faces. The data come from Kelley et al. (1998). Bars indicate standard error of the mean (SEM). Signal intensities were calculated by comparing each memorization task to a baseline fixation control task. The pattern of activation shown here is markedly different from the pattern of activation observed in the dorsal frontal cortex.

tern—words remembered better than faces—was observed following right-hemisphere anesthesia. Moreover, recognition was essentially at chance for word memory following left-hemisphere anesthesia and for face memory following right-hemisphere anesthesia.

The results are also consistent with findings from previous lesion studies (Gazzaniga & Smylie, 1983; Jones-Gotman & Milner, 1977; Milner & Taylor, 1972). For example, “split-brain” patients—epileptic individuals who have had the corpus callosum severed to minimize the spread of seizure activity—perform significantly better on tests of face memorization when the faces are presented to the right hemisphere than the left hemisphere (Gazzaniga & Smylie, 1983).

But can material-specific memory impairments be related to frontal activity? Patients with frontal lesions often perform well on certain tests of memory such as simple recognition. However, there is some evidence to suggest that isolated frontal lobe lesions cause material-specific memory impairments. Patients with left frontal lobe lesions have been shown to perform poorly on recognition tests of studied words, whereas patients with right frontal lobe lesions have shown impairments for remembering nonverbal materials such as pictures and bird songs (Whitehouse, 1981; Riege, Metter, & Hanson, 1980). There are several possible explanations for the apparent discrepancies across studies. First, many lesion studies have examined patients with chronic or long-standing lesions. One possibility is that over time, compensatory brain pathways may mediate task performance in these patients. For example, Buckner et al. (1996) demonstrated that the right frontal cortex may compensate for lesions to the left frontal

cortex (including Broca's area) to permit normal performance on certain speech production tasks. The "reversible lesions" induced during Wada testing differ from traditional lesion studies by permitting immediate postlesion language and memory assessment. Such testing is presumably less susceptible to possible compensatory mechanisms that may be acting in patients with chronic lesions.

Second, many studies that report intact memory performance following frontal lesions often exclude patients with damage to more posterior, dorsal frontal regions shown to be active in imaging studies of memory. This is particularly true for patients with left hemisphere lesions because these patients often exhibit verbal processing deficits.

More recently, functional neuroimaging studies have demonstrated that the level of activity in certain frontal regions can predict, on average, whether an item will later be remembered or forgotten (Brewer et al., 1998; Wagner, Schacter, et al., 1998), and these effects are also found in different hemispheres based on material type.

In the present study, inspection of the angiography images revealed that while MCA filling was robust in each patient, PCA filling was minimal for most of the individuals tested. These data are consistent with findings from previous single photon emission computed tomography (SPECT) studies (Kim, Lee, Nam, Song, & Lee, 1999; Urbach et al., 1999; Jeffrey et al., 1991). These studies strongly suggest that (in the absence of a direct "fetal" origin of the PCA from the ICA) an amytal injection into the ICA does not perfuse most of the medial temporal lobe, including most of the hippocampus and its associated cortex, but does anesthetize other cortical regions including the frontal and parietal cortex. Collectively, these findings have obvious implications for the utility of the ICA Wada test in predicting memory deficits posthippocampectomy. In fact, the test is only somewhat predictive of significant verbal memory deficits (Dodrill & Ojemann, 1997) perhaps because of the findings described here.

In spite of these findings, other studies have demonstrated that although the posterior hippocampal regions are not directly perfused by an ICA amytal injection, there can be noticeable functional changes in these regions. For example, a SPECT study by Kim et al. (1999) revealed decreased regional cerebral blood flow in the posterior portion of the hippocampus following ICA amytal injections. The SPECT study further revealed infrequent delivery of amytal to this region. Similarly, Urbach et al. (1999) combined SPECT imaging and depth electrode recordings and observed slowing in the posterior portion of the hippocampus (as evidenced by stereo-EEG activity change), even though SPECT imaging demonstrated that ICA amytal rarely perfused this region. These observations leave open the answer to the following question: If sodium amytal does not reach

most of the medial temporal lobe, why might activity in this region decrease?

One possible explanation for such findings is that inactivation of other brain regions caused by the direct effect of sodium amytal may have resulted in functional deafferentation of (or diaschisis in) medial temporal lobe regions. Put differently, slowing in the posterior hippocampal regions may be caused indirectly by the sudden disruption of critical neuronal inputs from regions directly affected by the drug. Thus, for the patients studied here, it is a reasonable possibility that the observed memory impairments resulted from anesthesia to regions outside the medial temporal lobe. These impairments could be directly related to the effects of amytal on specific mnemonic processing in these regions, or more likely, the processing engaged by these regions may be a critical input required by the medial temporal lobe for successful memory formation.

So which cortical regions provide this critical input and, as a result, contribute to the memory impairments seen during the ICA Wada test? Based on the unequivocal distribution of sodium amytal to both frontal and parietal regions and the possible distribution to anterior portions of the temporal lobe via the anterior choroidal artery, one could speculate that the memory impairments described here may have resulted from anesthetization of either the frontal, parietal, or perhaps, anterior temporal regions. However, inspection of the functional imaging results indicates that the parietal activations observed during intentional memorization of words and faces, at least in the Kelley et al. (1998) study, do not follow the same lateralized pattern of activation observed in the frontal regions. Specifically, parietal activity was greatest for faces in both hemispheres. This would suggest that if parietal activity was critical to successful memory formation, faces would be more difficult to memorize than words following both left and right hemisphere anesthesia.

Alternatively, it could be argued that anesthetization of the anterior temporal regions including the anterior tip of the hippocampus (via the anterior choroidal artery) induced posterior hippocampal slowing that then led to selective verbal/nonverbal memory impairments. That is, by simply inactivating the anterior tip of the hippocampus, the entire hippocampal formation is rendered functionless. This notion has received some support in the literature (Kim et al., 1999; Urbach et al., 1999; Gotman, Bouwer, & Jones-Gotman, 1992), and it is somewhat difficult to reconcile this possibility with one that implicates other cortical regions. This idea would be particularly appealing if the ipsilateral posterior hippocampus was the only brain region that showed slowing following ICA amytal injections. If that were true, then the results presented here could be explained strictly in terms of medial temporal involvement.

However, the literature suggests that slowing is non-specific. Gotman et al. (1992) report that many areas

show slowing following unilateral ICA amytal injections, including both ipsilateral and contralateral brain regions, regardless of whether the region was irrigated by the ICA. Specifically, regions that exhibited slowing included structures within the vascular distribution of the ICA (e.g., ipsilateral frontal cortex, parietal cortex, and anterior temporal regions) as well as regions outside the distribution of the ICA (e.g., ipsilateral medial temporal regions and occipital cortex, in addition to contralateral frontal, parietal, medial temporal, and occipital regions). Thus, the slowing observed in the posterior hippocampus may be related to a more global, whole-brain phenomenon. If so, one might expect any memory deficits resulting from this global slowing to be non-specific (i.e., not hemisphere-dependent). In fact, this general slowing might account for the overall reductions in memory performance following administration of amytal as compared to baseline performance. However, we also observed specific memory deficits, and it is somewhat unclear how global slowing can account for these data. On the other hand, the material-specific memory impairments observed here converge nicely with the pattern of activation observed with fMRI in frontal regions during intentional memorization of words and faces.

Taken in combination with the neuroimaging findings, the results described here suggest that, much like the medial temporal lobes, the participation of the frontal cortex is crucial to successful memory formation. The lack of participation of the left frontal cortex may disrupt memory formation for verbal materials; the lack of participation of the right frontal cortex may disrupt memory formation for nonverbal materials. As a result, memory formation seems to depend on the joint participation of the frontal and medial temporal lobe structures. Our speculation would be that memory formation may occur only when the frontal cortex provides a source of information to the medial temporal lobe. The medial temporal lobe may function to bind together or associate the outcomes of information processed in the frontal and other cortical regions to form lasting memory traces. According to this view, both regions would be necessary for successful memory formation, and the lack of participation of either brain region would impair memory formation (for review see Buckner, Kelley, & Petersen, 1999).

Finally, the results presented here illustrate how information obtained using functional neuroimaging techniques can be used synergistically with lesion-behavior studies. In this particular instance, fMRI findings permitted strong hypotheses regarding the importance of the frontal cortex to memory formation that were subsequently addressed using the Wada test. By integrating results across both techniques, a richer understanding of the neural architecture of memory formation was achieved than could have been achieved using either technique in isolation.

## METHODS

### Patients

Sodium amobarbital angiography (Wada testing) was performed on 21 patients (10 men, 11 women) aged 19 to 49 years (mean age = 35) as part of a comprehensive evaluation for potential neurosurgical treatment. The majority of these patients (18) were undergoing preoperative evaluation prior to unilateral temporal lobe resection. All patients underwent conventional MRI. Patients with seizure disorders also underwent positron emission tomography (PET) and closed circuit television and scalp electroencephalographic monitoring studies. This report focuses only on the Wada test.

### Wada Procedure

After placement of a 5 French femoral arterial sheath, a 5 French cerebral catheter (H1 or HN4, Cook, Bloomington, IN) was used to select the ICA ipsilateral to the proposed surgery. An internal carotid injection of non-ionic contrast material (Opitray 320, Malinckrodt Medical, St. Louis, MO) was performed to image the cerebral vasculature with biplane digital subtraction equipment (NeuroStar, Siemens, Erlangen, Germany). Providing no persisting fetal connections to the vertebral or basilar artery were demonstrated, the catheter position in the ICA was confirmed and sodium amytal (amobarbital) was injected. In one patient, angiography revealed a persistent trigeminal artery in the right hemisphere. In this patient, a microcatheter was advanced beyond the trigeminal artery to avoid injection of amytal into the vertebrobasilar system. Amytal was dissolved in sterile water (50 mg/ml) and delivered as a bolus over 2–4 sec. The average dose administered was 103 mg ( $SD = 10$  mg) in each ICA. The catheter was removed from the sheath immediately after a physiological effect was observed. Approximately 1 min prior to injection, neuropsychological testing was begun. After a delay of 30 min to allow for near complete metabolism of the amytal, the procedure was repeated in the opposite hemisphere. For each patient, the same dose of amytal was always administered to both hemispheres.

Testing was performed three times: before entry into the angiography suite to obtain baseline scores and to familiarize the patients with the procedure (BASELINE), during administration of amobarbital to the left hemisphere via the LICA, and during administration of amobarbital to the right hemisphere via the RICA. The order of LICA and RICA testing varied across patients (testing was always performed first on the side of the proposed operation). The baseline test lasted approximately 7 min. For the LICA and RICA phases, neuropsychological testing was begun 1 to 2 min before injection of amytal. Testing continued until the patients' performance returned to baseline levels, as evidenced by normal

mental status, comprehension, speech production, and grip strength.

The neuropsychological testing procedure was a modification of the procedure used by Dodrill (1993) and consisted of two parts: a language/short-term memory task and a long-term memorization task. During the language task, patients were asked (1) to name a visually presented object (e.g., a fork), (2) to read a sentence printed on a card (e.g., "Fur grows on dogs."), and (3) to recall the name of the recently presented object. This sequence was repeated continuously as quickly as the patient could perform the tasks. A set of 20 objects and 40 sentences were used for this task. One minute after injection, the language task was interrupted and a portion of the memorization task was conducted. During this time, patients were shown a word for approximately 3 sec and then an unfamiliar face for another 3 sec (the order of word/face presentation was counterbalanced such that half the time a word was presented first and half the time a face was presented first). Patients were instructed to remember each item for later. Following the presentation of both items, the language task was resumed for another minute until the next word and face were presented. In total, each patient viewed four novel words and four novel faces during each test (with presentations of one word and one face at approximately 2, 3, 4, and 5 min after the start of the language task). In instances where speech suppression was still apparent 3 min after injection, the third set of items was presented following the first correct naming of an object. The fourth set of items was presented after three consecutive objects were named correctly.

When the patients' performance on the language task returned to baseline levels, the neuropsychological procedure was terminated and a yes/no recognition memory test was administered. During the memory recognition test, patients were shown eight words and eight faces. Half of the words and faces were "old" items that the patients had studied during the memorization task. The remaining half were "new" words and faces that had not been previously presented. For each item, patients indicated, by saying "yes" or "no," whether they remembered seeing the item during the procedure. The entire procedure was performed in a uniform fashion for all patients by the same neuropsychologist. For each subject, the LICA and RICA phases of the procedure were videotaped and checked for accuracy.

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