Presurgical Language Mapping

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ABSTRACT—*Neurosurgical procedures for tumors or intractable epilepsy are often accompanied by risk to postoperative cognitive function; surgery in the left temporal or frontal lobes, for example, can place language functions at risk. Hence, prior to tissue extraction, one common surgical goal is to attempt to identify frontal and temporal regions that should be spared in order to preserve language function. We describe how basic research on false memory for word lists has led to a novel approach for identifying such language-related regions in healthy controls. That is, rapid presentation of semantically related words (e.g.,* bed, rest, awake*) and phonologically related words (e.g.,* peep, weep, heap*) with instructions to attend to relations among the words elicits activity in underlying language networks. Furthermore, it is often possible to identify the neural underpinnings of these networks in an individual person in about an hour of functional magnetic resonance imaging (fMRI) scanning. We conclude by suggesting directions for future research with this lexical-processing protocol, the overarching goal being to link basic cognitive science and clinical practice.*

KEYWORDS—*language; neuroimaging; false memory; fMRI; semantic; phonological*

This article describes a link between basic cognitive psychological research on false memories and an important clinical problem: the localization of cortical language regions in individual neurosurgical patients. We begin by outlining the clinical goal and then we explain how an ostensibly unrelated line of research on memory illusions may have implications for this problem. We end by considering how future research may pave the way for a direct application to clinical practice.

LOCALIZATION OF LANGUAGE WITHIN NEUROSURGICAL PATIENTS: CURRENT APPROACHES

Neurosurgical procedures such as tumor resection (extraction) or epilepsy surgery can expose language abilities to impairment, especially when the procedures are performed in dominant-hemisphere (typically left-hemisphere) frontal or temporal lobes (in or near what have historically been called Broca's and Wernicke's areas, respectively). The precise location of these regions varies across individual patients (G. Ojemann, J.G. Ojemann, Lettich, & Berger, 1989). For this reason, surgery is often guided by patient-specific information regarding language localization. The guiding principle behind this emphasis on language localization prior to resection is that compromised linguistic abilities are generally considered least acceptable to patients (among a range of possible cognitive impairments that could arise from neurological surgery) and that severe aphasia would be a particularly undesirable outcome compared to other possible impairments.

Brain tumors are often invasive of normal brain tissue and cannot be distinguished by sight alone. Further, as the brain is invaded, function can be retained for some time (J.G. Ojemann, Miller, & Silbergeld, 1996). Thus, the balance between aggressive surgical resection and quality of life is best addressed with information about cortical function. Here we focus primarily on localizing and sparing temporal-lobe contributions to language function.

Which hemisphere controls language function in a particular patient is often assessed by administering the intracarotid amobarbital test, commonly known as the Wada test. This approach invokes a temporary disruption of first one and then the other hemisphere while the patient performs a language task (often the naming of pictures of common objects). The goal is to uncover which hemisphere seems to be critical for language function by observing deficits obtained when only one hemisphere is able to function. Hence, at best, this approach reveals whether a patient is right- or left-dominant for language; it does not specify critical locations for language within a given hemisphere. A further downside to the technique is that it is invasive, requiring an injection into the patient's carotid arteries (which lead from the heart to the brain). Various language protocols using functional magnetic resonance imaging (fMRI) have been developed to try to supplement or replace the Wada test (e.g., Desmond et al., 1995), but the use of neuroimaging in the clinical setting has not yet been universally accepted.

Currently, to localize language regions within a given hemisphere with the goal of safe surgical intervention, invasive measures must be taken. Either before surgery, using an

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implanted electrode array, or at the time of surgery (with the patient awake), cortical-stimulation mapping (CSM) can identify critical language areas.

If done at the time of surgery, the patient is initially sedated, their scalp anesthetized, a section of the skull removed, and the dura opened to expose the cortical surface. The patient is awakened intraoperatively and asked to perform a language task while small amounts of electrical current are applied to specific cortical regions (Fig. 1). The electrical current produces a temporary, spatially-specific (within 1 square centimeter) disruption in function of the stimulated region (lasting 4 seconds or fewer), while the task is performed. As in the Wada test, a typical procedure would require the patient to attempt to name pictures of common objects. To the extent that a stimulated site is critical for language function, picture naming will be disrupted during stimulation. Such disruption could be manifested as a temporary lack of ability to speak or as an error (e.g., calling a pencil a stick). However, if the stimulated site is not necessary for the language task, no disruption will be observed. In this way, the surgeon can identify regions to spare during the immediately following surgical removal of tissue. CSM has consistently demonstrated the importance of regions within the left temporal and parietal cortices for language function, although it is noteworthy that the exact location of these regions within the temporal and parietal cortices may vary considerably across patients (G. Ojemann et al., 1989).

The CSM approach is in some ways very attractive. Surgery guided by CSM has good outcomes in terms of language preservation (Haglund, Berger, Shamseldin, Lettich, & G. Ojemann, 1994), and it is widely considered by clinicians to be the "gold standard" for identifying language regions in the neurosurgical setting. It is less than ideal, however, for several reasons. First, in order for a surgeon to perform CSM, a patient must be awakened during the operation and asked to name pictures coherently, a

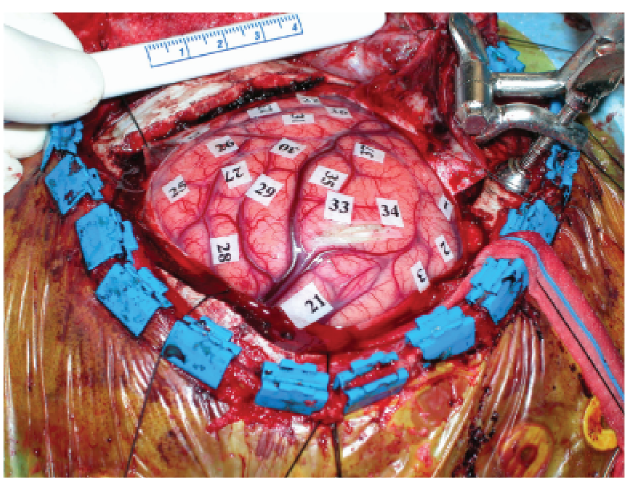

Fig. 1. Exposed brain of a patient undergoing cortical-stimulation mapping (CSM). Numbers correspond to labels that guide stimulation mapping during surgery.

prospect that is unacceptable or even impossible for some patients. Further, the procedure is time consuming (taking approximately 30 minutes or so for language mapping), invasive, costly, and cannot be revisited if results are ambiguous. In this light, noninvasive methods like fMRI that could identify language regions prior to surgery would be very valuable clinically. For example, with fMRI it may be possible to determine how close language function is to the proposed site of tissue resection before surgery is even undertaken.

THE CLINICAL GOAL: NONINVASIVE, PRECISE, AND PREOPERATIVE ASSESSMENT OF LANGUAGE FUNCTION

Since the introduction of functional neuroimaging techniques (especially fMRI), clinicians have sought to use imaging procedures clinically as a noninvasive way of localizing language function in neurosurgical patients prior to surgery (with the eventual goal of supplementing, or potentially even replacing, CSM). To be useful for neurosurgeons and their patients, an fMRI language protocol would need to satisfy at least five criteria: (a) It would need to elicit reliable, robust language-related activity in individuals; (b) it would need to activate language sites in both the frontal and temporal cortices; (c) it would need to be usable with various clinical populations (e.g., a wide range of age or intelligence levels); (d) it would need to be quick enough that the preoperative scanning session would be well tolerated by most patient groups; and finally, (e) language regions identified by the fMRI technique would need to align with regions identified by the current gold-standard approach of CSM.

Thus far, neuroimaging language protocols have not been able to meet these criteria. One problem is that although fMRI studies of language have been very informative for identifying the neural substrates of language at the group level (where averages are computed across 15 to 20 subjects), obtaining reliable, robust activation of language regions for individual participants has proven to be a more daunting task. An additional complication is that although it is well documented that lesions to the middle and superior temporal gyri can lead to comprehension deficits (Bates et al., 2003), neuroimaging studies of single-word reading do not always strongly reveal activity in these regions, even at the group level (Petersen, Fox, Posner, Mintun, & Raichle, 1988). Further, picture naming, the task typically used during CSM to map language, does not produce particularly robust activity in temporal or parietal language regions (which may reduce the correlation observed between imaging protocols of language function and CSM). This puzzling trend could be due in part to the fact that specific language sites vary across people (G. Ojemann et al., 1989), a situation that underscores the need for precise language identification in individuals. Hence, identification of an fMRI protocol that could strongly activate frontal and temporal language regions within individuals in a short period of time would seem to be a good starting point for the development of a clinically useful tool. We describe below a research line on associative memory illusions that led us to the development of a technique that we believe approaches this goal.

THE BASIC RESEARCH: AN ASSOCIATIVE MEMORY ILLUSION

When people are presented with a set of about 15 semantic associates (e.g., *bed*, *rest*, *awake*), all of which converge upon a related, nonpresented word (e.g., *sleep*) there is a high likelihood of recalling or recognizing having heard the related word even though it was not presented (Roediger & McDermott, 1995). Similarly, when presented with a set of phonological associates (e.g., *beep*, *weep*, *heap*), all of which sound similar to a nonpresented word (e.g., *sleep*), people tend to recall or recognize having heard the related, nonpresented word. The literature spawned by this phenomenon is typically classified as "false memory" research. For the purpose of the present paper, it is noteworthy that the mechanisms behind the phenomenon appear to be linguistic in nature. Specifically, false recall and false recognition result at least in part from spreading activation (Collins & Loftus, 1975), whereby related concepts are linked in semantic memory such that accessing one concept (e.g., *bed*) initiates activation across the linked pathways and thereby activates related concepts (e.g., *sleep*). The spread of activity throughout the associative network leads to priming of related concepts, making these primed concepts more easily accessible, to the point of being "remembered" (McDermott & Watson, 2001; see Roediger, Balota, & Watson, 2001, for a review).

IMAGING LANGUAGE NETWORKS

To the extent that the origin of these false-memory phenomena is indeed the spread of activation among associates in underlying semantic and phonological language networks, one might expect clear activity in frontal and temporal language regions during the encoding of these word lists. Specifically, a contrast of the activation observed during silent reading of semantically associated and phonologically associated lists might be expected to dissociate the underlying neural substrates of semantic and phonological processing, respectively. To test this possibility, we (McDermott, Petersen, Watson, & J.G. Ojemann, 2003) presented 20 healthy young adults with 36 lists of 16 semantically associated words and 36 lists of 16 phonologically associated words at a quick pace (about 500 ms per word, which left little time for extraneous processing of alternate dimensions of the stimuli). To further challenge the systems of interest, our participants were instructed to focus on the meaningful relations for the lists of semantic associates and the sound-based relations for the lists of phonological associates. As predicted, the results of our fMRI study revealed robust semantic and phonological processing differences in underlying frontal and temporal language networks. Specifically, as shown in Figure 2, we found that at both the group level and at the level of individual participants, a contrast of the encoding of the two list types (semantic vs. phonological) produced clear activation preferential for semantic processing in the left inferior frontal and left middle or superior temporal cortices.

This finding represents an important step forward in that it was obtained with a short lexical-processing protocol (about an hour of functional scanning), which elicited robust activation in the left temporal cortex. As discussed previously, these features are

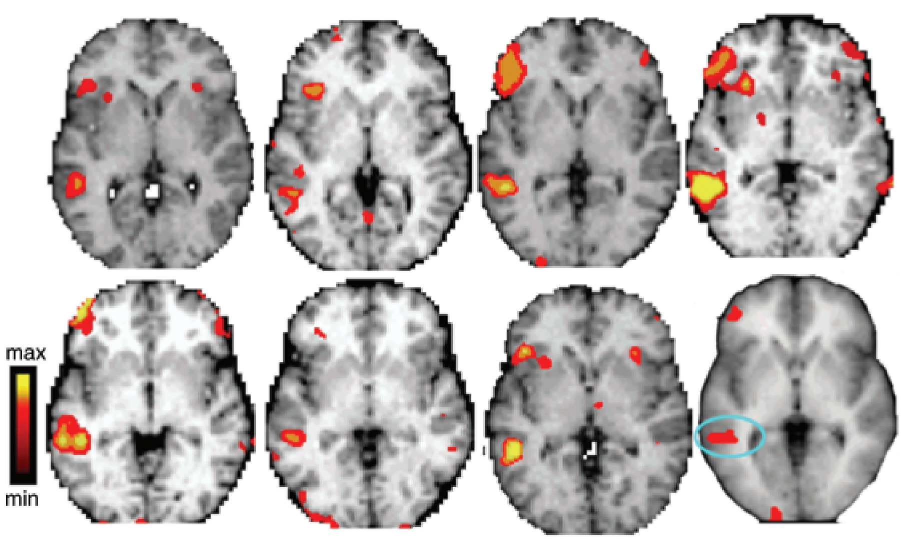

Fig. 2. Regions in the frontal and temporal cortices that were preferentially active (colored patches) for semantic processing (relative to phonological processing) for 7 of the 20 individual subjects in the study by McDermott et al. (2003). The regions identified by the group analysis are depicted in the bottom right corner (temporal activation circled in blue).

critical for the endeavor of using imaging data to enhance surgical planning. Further, and also critical, is the finding of interpretable activity within individuals. Indeed, we saw in all 20 of our subjects activation preferential for semantic (over phonological) processing in the inferior frontal and temporal cortices.

However, as noted earlier, for an fMRI language protocol to be clinically useful to neurosurgeons and their patients, it would not only have to be short and give robust frontal and temporal language-related activity at the level of individuals, but it would also need to satisfy at least two other constraints: Specifically, the protocol would have to be useable in various clinical populations (e.g., a wide range of age or intelligence levels), and the fMRI results would need to correlate with the current gold-standard approach of CSM. To address these and other issues, we now briefly consider several lines of future research, the overarching goal being to link basic cognitive science on lexical processing and clinical practice.

FUTURE DIRECTIONS

The observation that the McDermott et al. (2003) fMRI language protocol elicited activity in frontal and temporal cortices in individual healthy young adults is certainly encouraging. In this light, one potentially promising line of future research with this protocol would be to evaluate the extent to which activity in individual patients' fMRI data correlates with the CSM results obtained during surgery. All surgical procedures would be guided by CSM, but in essence the question to be asked is: If the procedures were to be guided by fMRI with the lexical fMRI protocol, would they be performed any differently?

Several interrelated empirical questions could also be addressed in the context of the proposed program of research that combines fMRI and CSM methodologies. For example, how reliable are the language-processing regions identified by fMRI? It may be necessary to scan each patient at least twice with the fMRI protocol to determine whether activations in frontal and temporal cortices are reliable (and hence more likely to correlate with the results of CSM). In addition, one might ask what statistical-significance threshold or multiple-comparison correction procedure is reasonable to use on imaging data when evaluating the match between fMRI and CSM results. Further still, one might ask whether it is better to use statistical comparisons that reveal regions activated by both semantic and phonological processing (as opposed to dissociating the underlying networks with the contrast of semantic and phonological processing, as depicted in Fig. 2). The idea is that some statistical comparisons (e.g., semantic vs. baseline, phonological vs. baseline, or semantic and phonological combined vs. baseline) might be more optimal for revealing robust activity in language regions in some patients than others (which may in turn be related to individual differences in age, verbal ability, intelligence, or other factors). Certainly, there may be other intriguing lines of research that could follow from this question, as well.

CONCLUSIONS

In summary, this article has described a potential direct link between basic science—specifically, the elucidation of mechanisms leading to false memories following presentation of associative word lists—and clinical science—specifically, the planning of neurosurgery. Strong theoretical understanding of the mechanisms underlying false memories for related associates led to a neuroimaging experiment on the topic of language organization, which, in turn, may have strong implications for clinical science and practice.

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