



Mapping anterior temporal lobe language areas with fMRI: A multicenter normative study

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ABSTRACT

Removal of the anterior temporal lobe (ATL) is an effective surgical treatment for intractable temporal lobe epilepsy but carries a risk of language and verbal memory deficits. Preoperative localization of functional zones in the ATL might help reduce these risks, yet fMRI protocols in current widespread use produce very little activation in this region. Based on recent evidence suggesting a role for the ATL in semantic integration, we designed an fMRI protocol comparing comprehension of brief narratives (Story task) with a semantically shallow control task involving serial arithmetic (Math task). The Story > Math contrast elicited strong activation throughout the ATL, lateral temporal lobe, and medial temporal lobe bilaterally in an initial cohort of 18 healthy participants. The task protocol was then implemented at 6 other imaging centers using identical methods. Data from a second cohort of participants scanned at these centers closely replicated the results from the initial cohort. The Story–Math protocol provides a reliable method for activation of surgical regions of interest in the ATL. The bilateral activation supports previous claims that conceptual processing involves both temporal lobes. Used in combination with language lateralization measures, reliable ATL activation maps may be useful for predicting cognitive outcome in ATL surgery, though the validity of this approach needs to be established in a prospective surgical series.

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Introduction

Partial removal of the anterior temporal lobe (ATL) remains the most common surgical procedure performed for treatment of intractable epilepsy and is effective at stopping seizures in a majority of patients (Tellez-Zenteno et al., 2005; Wiebe et al., 2001). Postoperative decline in naming or verbal memory ability is observed in roughly 30–50% of patients after left ATL resection (Baxendale et al., 2006; Bell et al.,

2000; Binder et al., 2008a; Chelune et al., 1993; Gleissner et al., 2004; Helmstaedter and Elger, 1996; Hermann et al., 1994; Langfitt and Rausch, 1996; Lee et al., 2002; Lineweaver et al., 2006; Sabsevitz et al., 2003; Stroup et al., 2003). The magnitude of these declines is related to the degree of language lateralization to the left hemisphere and can be predicted using preoperative functional magnetic resonance imaging (fMRI) (Binder et al., 2008a; Sabsevitz et al., 2003).

fMRI might also be useful for “tailoring” resections to avoid critical language zones in the ATL. This application of fMRI, however, rests on two critical assumptions: that activated areas are functionally necessary and should not be resected and that inactive areas are functionally unimportant and therefore safe to resect. The former

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assumption is problematic because activation may reflect a variety of processes and does not necessarily indicate that the activated region is critical for the cognitive outcome of interest. The latter assumption is particularly problematic because different fMRI language contrasts vary dramatically in their ability to identify functionally active tissue in the ATL (Binder et al., 2008b; Visser et al., 2010). Though there is an extensive literature on activation of the medial ATL (anterior hippocampus and parahippocampus) using episodic memory encoding and retrieval tasks (see, e.g., Hwang and Golby, 2006; Paller and Wagner, 2002; Rugg et al., 2002; Schacter and Addis, 2007 for reviews), methods for activating ventral, lateral, and polar regions of the ATL are less well defined. Most fMRI language paradigms in widespread clinical use produce little or no activation of these regions (Benson et al., 1999; Binder et al., 2008b; Jansen et al., 2006; Lehericy et al., 2000). The validity of tailoring resections using fMRI maps thus depends on the activation protocol used to generate these maps. Another factor that can impair fMRI sensitivity in the ATL is signal loss due to macroscopic field gradients, which commonly affects specific regions of the ATL (Devlin et al., 2000; Ojemann et al., 1997).

Considerable functional imaging and neuropsychological evidence suggests a role for the ATL in semantic processing, that is, storage and retrieval of conceptual knowledge that underlies word meaning (Binder et al., 2009; Mummery et al., 2000; Patterson et al., 2007; Rosen et al., 2002; Visser et al., 2010). Damage to this semantic system has been proposed as a major cause of the naming deficits observed in patients with ATL damage (Bell et al., 2001; Lambon Ralph et al., 2001). Recent studies suggest several factors that influence the detection of these ATL areas with fMRI. First, the ATL is more strongly activated by sentences than by single words or strings of unrelated words (Friederici et al., 2000; Humphries et al., 2006, 2005; Mazoyer et al., 1993; Vandenberghe et al., 2002; Visser et al., 2010; Xu et al., 2005). This observation suggests that at least some parts of the ATL are involved in multiword integration processes unique to sentence comprehension tasks (Jung-Beeman, 2005). Comprehension of sentences, and particularly of longer forms such as narratives and discourse, requires not only rapid retrieval of conceptual representations but also integration of individual concepts to form complex scenes with actors, intentions, and events. Thus there is also evidence for involvement of the ATL in comprehension of social interactions (Olson et al., 2007; Ross and Olson, 2010; Zahn et al., 2007), which likely depends on a similar rapid integration of conceptual information. Activation in these studies typically involves polar and superior aspects of the ATL bilaterally. Second, ATL activation is more likely to be observed when an active control task is used as a baseline rather than a resting state (Binder et al., 2008b; Spitsyna et al., 2006; Stark and Squire, 2001; Visser et al., 2010). For example, Stark and Squire (2001) observed activation in medial ATL regions during a picture encoding task when an active decision task was used as a baseline but not when a “rest” baseline was used. Similarly, Spitsyna et al. (2006) observed activation in the anterior fusiform gyrus and ITG during a story comprehension task when an active decision task was used as a baseline but not when a “passive” baseline was used. This observation suggests that semantic and episodic memory processes carried out by the ATL occur even during resting or passive states, comprising a component of normal consciousness that supports planning, problem solving, daydreaming, and other high-level integrative processes that depend on semantic knowledge (Binder et al., 2009; Binder et al., 1999). Active, attentionally-demanding control tasks disrupt these ongoing “default” processes, which would otherwise mask ATL activation.

Given the potential clinical benefits of using fMRI to tailor ATL resections, there is a critical need to define a reliable and sensitive fMRI task paradigm for this purpose. Our aim in the current study was to develop such a method and test its effectiveness at identifying ATL language zones in individual subjects. Based on prior studies of the ATL reviewed above, a story comprehension task was selected to

engage rapid integration of conceptual information, including social concepts. This task was contrasted with an active, attentionally demanding arithmetic task. Prior evidence indicates that calculation tasks, particularly addition and subtraction operations, do not engage the temporal lobe (Baldo and Dronkers, 2007; Cappelletti et al., 2001; Crutch and Warrington, 2002; Diesfeldt, 1993), thus this task was expected to interrupt ongoing “default mode” processing in the ATL and to cause minimal ATL activation. An additional feature of the arithmetic task is that it used verbal, sentence-like stimuli that could be matched to the stories on low-level features like auditory and phonological input. A second aim of the study was to test whether comparable results could be achieved at different centers with a variety of imaging hardware and software platforms, as this is a prerequisite for any test under consideration for clinical application. It was not our aim to test different pulse sequences for optimal ATL coverage, to investigate alternative data analysis methods, or to examine effects of thresholding at different levels, though these are all important topics for future research.

Methods

Participants and centers

Participants in the study were 34 healthy, right-handed adults (17 women and 17 men), aged 18–50 years (mean 29 years). All spoke English fluently and had no history of neurological illness. In the initial development phase, 18 of these participants were scanned at the Medical College of Wisconsin (MCW). Subsequently, 2–3 additional participants were scanned at each of the following six centers to create a Multicenter cohort: Cleveland Clinic Foundation, Cleveland, OH (CCF); Georgia Institute of Technology, Atlanta, GA (GT); Medical University of South Carolina, Charleston, SC (MUSC); University of Cincinnati, Cincinnati, OH (UCin); University of Rochester, Rochester, NY (UR); and University of Washington, Seattle, WA (UW). The MCW and Multicenter cohorts were matched on age, sex, and education. All participants gave informed consent according to local institutional guidelines.

Tasks and stimuli

Identical stimuli and E-Prime (Psychology Software Tools, www.psnet.com) scripts were used at each center. All stimuli were presented aurally using MRI-compatible headphones adjusted to a comfortable listening level. Participants kept their eyes closed during all functional scans.

Story task

The language task required attentive comprehension of brief stories adapted from a collection of Aesop's fables (www.aesopfables.com). Spoken versions of the stories were generated using a text-to-speech synthesizer (MacinTalk male “Alex” voice in Mac OS X 10.5), which enabled control over word rate, speaking style, and prosodic features. Stories were selected to be relatively brief (around 5–9 sentences) and engaging. All involved animal or human characters interacting in easily understandable social situations. Salient characteristics of the stories are listed in Table 1. After each story, the participant was queried about the general topic of the story in the form of a 2-alternative forced-choice question. For example, after a story about an eagle that saves a man who had done him a favor, participants were asked, “That was about *revenge* or *reciprocity*?” Participants pressed a button under the right index finger to select the first choice or a button under the right middle finger to select the second choice.

Math task

The control task was designed to engage participants' attention continuously in mental arithmetic. The materials were problems

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