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Bilateral inferior frontal language-related activation correlates with verbal recall in patients with left temporal lobe epilepsy and typical language distribution

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Summary Language fMRI has been used in the presurgical evaluation of drug-resistant temporal lobe epilepsy patients. Previous studies have demonstrated that left temporal lobe epilepsy (LTLE) patients with atypical language lateralization are at lower risk of postsurgical verbal memory decline, hypothesizing co-occurrence of verbal memory and language reorganization presurgically. Furthermore, it has been proposed that the recruitment of right frontal language-related areas is associated with the preservation of verbal memory performance in these patients. However, less is known about the correlation between these functions specifically in LTLE patients with left language dominance, although they are more prone to postsurgical verbal memory decline. The aim of the present study was to investigate whether the relationship between verbal memory scores and frontal language activation is also observed in LTLE patients with typical language dominance. Eighteen healthy controls, 12 right temporal lobe epilepsy patients and 12 LTLE patients with typical language distribution as assessed by an fMRI verbal fluency task were selected. Verbal memory scores were obtained from the patients' neuropsychological presurgical evaluation. Our results showed a positive correlation between verbal recall and activation of bilateral inferior frontal areas in LTLE patients. These results

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support the hypothesis of a link between language representation in inferior frontal areas and hippocampal functioning, and indicate that both hemispheres are related to the preservation of verbal memory in patients with hippocampal damage and typical language dominance.

Introduction

Memory decline is the most important cognitive dysfunction in temporal lobe epilepsy patients after surgery. Presurgically available information can help us to predict the probability of cognitive decline such as: lateralization of the epileptogenic focus, presence of hippocampal sclerosis, age of onset or neuropsychological performance (Hermann et al., 1992; Stroup et al., 2003; Baxendale et al., 2006). Language fMRI has also been used at the presurgical level since it may provide relevant information about the language-dominant hemisphere, and this information helps to evaluate the probability of cognitive deficits postsurgically.

The study of language lateralization is especially relevant in patients with left temporal lobe epilepsy (LTLE) as they are more prone to language and verbal memory deficits after surgery (Stroup et al., 2003; Baxendale et al., 2006). Previous studies have shown a reorganization of language function in these patients, characterized by higher probability of atypical language representation (i.e., bilateral or right language dominance) due to decreased activation in the left inferior frontal areas and increased activation in the right homologues (Adcock et al., 2003; Brázdil et al., 2005; Carpentier et al., 2001; Janszky et al., 2004; Powell et al., 2007; Rosenberger et al., 2009). LTLE patients with atypical language dominance are at lower risk for verbal memory decline postsurgically (Binder et al., 2008, 2010). Moreover, previous studies with IAP (Helmstaedter and Kockelmann, 2006; Kim et al., 2003) and fMRI (Thivard et al., 2005; Everts et al., 2009) have revealed that LTLE patients with atypical (bilateral or right) language dominance exhibited significantly better verbal memory scores presurgically than patients with typical (left) language dominance. Those authors have suggested that a plausible explanation for the preservation of verbal memory in patients with atypical language dominance is the co-occurrence of atypical language and atypical verbal memory lateralization.

However, none of these studies have explored the relationship between language representation and verbal memory scores specifically in LTLE patients showing typical language representation. This is clinically relevant since these are patients with a greater risk of verbal memory decline. Therefore, our interest in the present study was to evaluate whether bilateral or right frontal activation is also related to verbal memory performance specifically in these patients. It is important to keep in mind that typical language dominance does not mean lack of right hemisphere activation; indeed, right inferior frontal activation typically appears in language tasks in healthy controls (Price, 2010).

Hence, the aim of the present study was to put forward the hypothesis of a link between hippocampal functioning and language representation, evaluating whether the recruitment of frontal language areas is associated with the preservation of verbal memory in LTLE patients with typical language distribution. To this aim, a sample of unilateral temporal lobe epilepsy patients with typical language lateralization as assessed by an fMRI verbal fluency task was selected. Verbal memory scores and IQs were retrieved from the patients' neuropsychological presurgical evaluation. Based on the proposed link between hippocampal functioning and language representation, we hypothesized that activity in inferior frontal language-related areas would be related to verbal memory scores in LTLE patients with typical language distribution.

Methods

Participants

Forty-two participants with typical language lateralization (as obtained with an independent threshold method, see ''Lateralization Indices'' section for methodological details) were selected: 18 healthy controls (HC), 12 right temporal lobe epilepsy (RTLE) patients and 12 LTLE patients (demographic information is summarized in Table 1). All patients were candidates for surgery and were diagnosed with unilateral RTLE or LTLE. In each group, 9 out of 12 patients exhibited unilateral hippocampal sclerosis. In addition, one patient in the LTLE group demonstrated amygdalar sclerosis. The rest of the patients (2 LTLE and 3 RTLE) had no identifiable lesions in the structural data. All the participants were right-handed as assessed using the Edinburgh Handedness Inventory (Oldfield, 1971). None of the participants in the HC group had any psychiatric or neurological history.

Data on age of onset, duration, number of seizures per month and educational level were retrieved from the patient's clinical history, and appear in Table 1. There were no between-groups differences for any of the demographic variables ($p > 0.05$). Informed consent was obtained from each subject prior to participation. The research project was approved by the Universitat Jaume I Ethical Committee, and the HC group received monetary compensation for their participation.

Neuropsychological tests

Patients underwent an extended neuropsychological battery as part of the presurgical evaluation. Of the whole battery, two scores obtained from the Spanish version of the California Verbal-Learning Test (Benedet and Alejandre, 1998) were selected: the Learning Curve score (LC, total number of words recalled for all five initial learning trials) and the Long Delay Free Recall score (LDFR, the number of free recalled words after a 30-min delay). Furthermore, the Wechsler Adult Intelligence Scale III (WAIS-III) was used to evaluate general intellectual functions (Full Scale IQ, Verbal IQ and Performance IQ).

FMRI task

Participants performed the Verbal Fluency Task (VFT) according to the protocol used in previous studies (Sanjuán et al., 2010a; Gaillard et al., 2000). Before entering the scanner, participants practiced it overtly with a shorter version (2 min), but were instructed to