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# Lateralization of language function in epilepsy patients: A high-density scalp-derived event-related potentials (ERP) study

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HIGHLIGHTS

- Event-related potentials (ERPs) were used to assess receptive language function lateralization.
- Scalp-derived ERPs were recorded during 3 language tasks in epilepsy patients and controls.
- Language-ERPs were left-lateralized in all tasks and showed high concordance with fMRI.

ABSTRACT

*Objectives:* Language functional magnetic resonance imaging (fMRI) represents the clinical standard for language lateralization assessment in presurgical epilepsy evaluation, but still many patients experience postoperative language deficits. Event-related potentials (ERPs), especially the negative component around and after 400 ms, are related to language processing and could therefore represent a complementary method of language lateralization assessment.
*Methods:* Scalp EEG was recorded from 64 locations in 36 epilepsy patients and 37 controls during three visually presented language tasks: A short-term language memory task (differentiation memorized vs. unknown words), a phonological task (detection of rhymes in word pairs), and a semantic decision task (differentiation words vs. pseudowords). ERPs were analyzed in the 300 ms–800 ms epoch. Language fMRI was routinely obtained in patients.
*Results:* ERPs were significantly more negative over the left compared to the right hemisphere in all three tasks in patients and controls. Laterality indices showed highest concordance with fMRI for the Word/Pseudoword Task.
*Conclusions:* ERPs of language processing were lateralized to the left hemisphere in the majority of epilepsy patients and controls. In patients, single-subject laterality indices showed high concordance with fMRI results.
*Significance:* Results indicate that scalp-derived ERPs are a promising tool to investigate lateralization of language function in epilepsy patients.


## 1. Introduction

Epilepsy surgery offers an effective and safe treatment option for patients with medically refractory seizure disorders and leads to seizure freedom in 60–80% of patients. The goals of epilepsy surgery are on one hand to remove the epileptogenic zone, giving seizure freedom, but also to avoid causing neuropsychological deficits such as language or memory dysfunction (Binder et al., 2008; Sabsevitz et al., 2003). Thus, the accurate localization of essential brain regions, which are responsible for language and memory, as well as vision and motor function, is of the utmost importance.

Language fMRI represents the current clinical standard for assessment of language lateralization in presurgical epilepsy evaluation to optimize the outcome of surgery. Nevertheless, language or verbal memory deficits occur in about one third of patients following epilepsy surgery (Sabsevitz et al., 2003). Therefore, improvement of noninvasive methods is warranted in presurgical assessment of language localization.

A promising and cost-effective alternative is provided by high-density scalp EEG, essentially the use of event-related potentials (ERPs). Concerning language function, specifically the ERP interval

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ranging from around 300 ms to 800 ms after stimulus onset is of interest. This is typically of negative amplitude and includes the so-called N400 component (Kutas and Hillyard, 1980) and the late negative component (LNC; Grunwald et al., 1995). These components are suggested to represent lexical access (Lau et al., 2008), semantic integration (Franklin et al., 2007), and retrieval from semantic memory (Kutas and Federmeier, 2000). Evidence from neuroimaging suggests that language processing-related ERPs primarily arise from middle and anterior temporal as well as inferior frontal regions (Bookheimer, 2002; Dronkers et al., 2004; Lau et al., 2008). A lateralization effect of language-related ERPs has been described in healthy individuals, indicating higher ERP amplitudes over the language-dominant hemisphere (Spironelli and Angrilli, 2006; 2009). Investigations in epilepsy patients, who have a higher probability of atypical language representation (Kurthen et al., 1992), are scarce and usually derive from invasive recordings (Eulitz et al., 2000; Mainy et al., 2008; Wu et al., 2011).

The aim of this study was to investigate the hemispheric dominance of language function in medically refractory epilepsy patients and healthy controls by using high-density scalp-derived ERPs. Different language tasks were applied to address various aspects of language processing.

## 2. Methods

### 2.1. Subjects

Thirty-six epilepsy patients and 37 healthy controls were included in the study. All subjects were native German speakers. Edinburgh Handedness Inventory (Oldfield, 1971) indicated right-handedness in all subjects except for one patient and one control, who were left-handed. All patients suffered from drug-resistant focal epilepsy and were undergoing presurgical evaluation at the Department of Neurology of the Medical University of Vienna. Apart from epilepsy, they did not suffer from other neurological disorders. Patients routinely underwent language fMRI, which included a standard verb generation paradigm (Broca's area) and a semantic decision paradigm (Wernicke's area). The study was approved by the Ethics Committee of the Medical University of Vienna and written consent was obtained by all subjects.

### 2.2. EEG recordings

Scalp EEG was obtained by an EASY CAP recording cap (Falk Minow Services, Germany) with sintered Ag/AgCl ring electrodes, a 64 channel BrainAmp amplifier system and BrainVision Recorder Version 1.20 (Brain Products, Germany) from 64 standard locations according to a 10-10-system (American Clinical Neurophysiology Society, 2006). Recordings were digitized at 1024 Hz, referenced to FCz and re-referenced offline to the average reference. Electrooculogram (EOG) was recorded with electrodes placed below both eyes and aside the right eye.

### 2.3. Language EEG tasks

All language tasks were visually presented via a computer screen. Only single words were presented at a time for 1000 ms each, followed by a centered fixation cross during randomized interstimulus intervals of 1500 ms–2200 ms. Tasks were explained prior to recordings and test trials were performed.

#### 2.3.1. Continuous memory recognition task (CMRT; modified Sternberg Task)

To investigate short term verbal memory function, a modified Sternberg Task (Chao and Knight, 1996; Sternberg, 1966) was developed as an adapted version of the continuous memory recognition task used by Papanicolaou et al. (2004), who found concordant results of language magnetoencephalogram (MEG) and Wada test in epilepsy patients. Subjects were instructed to memorize a list of 5 abstract nouns, which then had to be recognized from a consecutive presentation of 90 words comprising 9 repetitions of the five memorized words (as well as 45 new/unknown words in random order). Stimuli had to be indicated as memorized or new/unknown word by clicking on the left or right mouse button, respectively, with their right index and middle finger.

#### 2.3.2. Rhyme detection task

The Rhyme detection task was developed to investigate semantic processing (Rugg, 1984) and was created following studies by Spironelli et al. (2006, 2009), who described ERP-based language lateralization effects in healthy subjects. Eighty word pairs of concrete nouns were subsequently presented and subjects were asked to indicate whether the two words had rhymed or had not rhymed by pressing the left or right mouse button (40 rhyme pairs, 40 non-rhyme pairs).

#### 2.3.3. Word/Pseudoword Task

A Word/Pseudoword Task was developed to investigate lexical retrieval. The discrimination between real words and so-called "Pseudowords" – which are strings of letters, that are easily pronounceable, but do not have an actual meaning – is a core feature of semantic processing and has previously been used in ERP experiments (Frishkoff et al., 2009). A total of 96 words (48 words, 48 pseudowords in random order) were presented and subjects were instructed to indicate the stimulus as a word or a pseudoword by clicking on the left or right mouse button.

### 2.4. Analysis

Recordings were analyzed using BrainVision Analyzer 2.0.4 (Brain Products, Germany). Data were visually inspected for blinks and other artifacts and respective periods were excluded from further analyses. EEG data were digitally filtered with a 0.1 to 10 Hz bandpass filter (12 dB/octave) and with a 50 Hz notch filter, all filters being Butterworth zero-phase filters. For ERP averaging, the continuous EEG signal was segmented into epochs ranging from 100 ms before to 1000 ms after each stimulus onset (Rhyme task: only second word of each wordpair), corrected to a 100 ms-prestimulus baseline. For all three tasks, only trials with correct responses were included in the analyses. Following visual inspection of grand average ERP waveforms, mean amplitudes of the epoch ranging from 300 ms to 800 ms after stimulus onset were calculated for further statistical analyses.

Statistical analyses were performed with Statistica (Version 7, StatSoft Inc., Tulsa, USA) and SPSS (Version 21 and 22, Armonk, NY) with an alpha level of 0.05. For assessment of language lateralization, regions of interest (ROI) were defined over frontotemporal areas. For each hemisphere, means of amplitudes of 12 electrodes were calculated (Left hemisphere: Electrodes F3, F5, F7, FC3, FC5, C3, C5, CP3, FT7, T7 TP7, TP9; Right hemisphere: F4, F6, F8, FC4, FC6, C4, C6, CP4, FT8, T8, TP8, TP10). Averaged amplitudes were normally distributed as indicated by Kolmogorov–Smirnov test.

Analyses were based on a 3 (Task; CMRT/Pseudoword/Rhyme) × 2 (Stimulus Type in the Language Task; Memorized-Unknown/Word-Pseudoword/Rhyme-No rhyme) × 2 (Lateralization; Left vs. Right) × 2 (Group; Patients vs. Controls) repeated ANOVA design with Group as a between factor. Subgroup analyses in the patient cohort were based on a 3 (Task; CMRT/Pseudoword/Rhyme) × 2 (Stimulus Type in the Language Task; Memorized-Unknown/Word-Pseudoword/Rhyme-No rhyme) × 2 (Lateralization;