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Strongly lateralized activation in language fMRI of atypical dominant patients—Implications for presurgical work-up

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Summary
Purpose: Functional magnetic resonance imaging (fMRI) is being used increasingly for language dominance assessment in the presurgical work-up of patients with pharmacoresistant epilepsy. However, the interpretation of bilateral fMRI-activation patterns is difficult. Various studies propose fMRI-lateralization index (LI) thresholds between ±0.1 and ±0.5 for discrimination of atypical from typical dominant patients. This study examines if these thresholds allow identifying atypical dominant patients with sufficient safety for presurgical settings.
Methods: 65 patients had a tight comparison, fully controlled semantic decision fMRI-task and a Wada-test for language lateralization. According to Wada-test, 22 were atypical language dominant. In the remaining, Wada-test results were compatible with unilateral left dominance. We determined fMRI-LI for two frontal and one temporo-parietal functionally defined, protocol-specific volume of interest (VOI), and for the least lateralized of these VOIs (''low-VOI'') in each patient.
Results: We find large intra-individual LI differences between functionally defined VOIs irrespective of underlying type of language dominance (mean LI difference 0.33 ± 0.35, range 0—1.6;

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15% of patients have inter-VOI-LI differences >1.0). Across atypical dominant patients fMRI-LI in the Broca's and temporo-parietal VOI range from −1 to +1, in the ''remaining frontal'' VOI from −0.93 to 1. The highest low-VOI-LI detected in atypical dominant patients is 0.84.
Conclusions: Large intra-individual inter-VOI-LI differences and strongly lateralized fMRI-activation in patients with Wada-test proven atypical dominance question the value of the proposed fMRI-thresholds for presurgical language lateralization. Future studies have to develop strategies allowing the reliable identification of atypical dominance with fMRI. The low-VOI approach may be useful.

Introduction

Atypical cerebral language organization is a well-described phenomenon in epilepsy patients (Kurthen et al., 1994; Loring et al., 1990; Saltzman-Benaiah et al., 2003; Weber et al., 2006b). Language organization can be rather complex. It can comprise various degrees of contributions of both hemispheres to intact language use including dissociated representations of expressive and receptive language functions between both hemispheres. Also partial redundancy of language functions in both hemispheres has been described (Kurthen et al., 1994; Helmstaedter et al., 1997). In the presurgical work-up of patients with pharmacoresistant epilepsies the existence of atypical dominance is clinically relevant. This accounts not only for surgery close to typically eloquent cortex. Risks for neuropsychological deficits after epilepsy surgery (in particular mesio-temporal surgery and callosotomy) rely on the underlying language dominance, too (for review see Helmstaedter, 2004)

Traditionally, language lateralization was performed with the Wada-test (or intracarotid amobarbital procedure; Wada and Rasmussen, 1960). Yet, numerous studies published over the last decades suggest that functional magnetic resonance imaging (fMRI) may be capable of replacing the Wada-test for the determination of language lateralization (Desmond et al., 1995; Binder et al., 1996; Hertz-Pannier et al., 1997; Benson et al., 1999; Fernandez et al., 2001; Spreer et al., 2002). Compared with the Wada-test, fMRI offers a number of advantages. It is non-invasive, which entails the virtual absence of morbidity risk. It is easily accessible. Its setup is comparatively simple. fMRI requires less staff and time effort than the Wada-test. Additionally, fMRI produces lower costs than the traditional Wada-test (Medina et al., 2004).

However, the results of recent studies question the uncritical replacement of the Wada-test by fMRI. The overall concordance between fMRI and IAP is estimated to be only ~90% (Detre, 2004), and recent studies show even more relevant discrepancies between fMRI- and Wada-test-based language lateralization on the single subject level (Lehericy et al., 2000; Woermann et al., 2003). A particular problem with fMRI lies in the mode of interpretation of bilateral patterns of BOLD activation. While the Wada-test is an inactivating method blocking the function of one hemisphere and allowing testing the functional reserve capacity of the non-anesthetized hemisphere, fMRI is an activation method. If fMRI shows bilateral activation this does not necessarily embody a bilateral distribution of language-essential cortex. Bilateral activation patterns can, for example, result from the detection of language-associated but not language-essential cortex contralateral to the dominant hemisphere (Desmond and Chen, 2002). Even when using optimized activation protocols aiming to subtract any unspecific neuronal activation from the contrast between the active and control condition (Binder et al., 1999; Hund-Georgiadis et al., 2001), it cannot be excluded that parts of the active cortex are not essential for intact language use. Further reasons for bilateral distribution of BOLD activation can be an unfavorable scanner signal-to-noise ratio, the sub-optimal setting of statistical thresholds set to discriminate voxels which are considered activated during the language-condition of the fMRI-protocol from voxels considered non-active (Desmond and Chen, 2002; Loring et al., 2002; Rutten et al., 2002; Jansen et al., 2006) and the renunciation of anatomically or functionally defined volumes of interest (VOIs), for which a lateralization index (LI) between both hemispheres is determined (Rutten et al., 2002; Spreer et al., 2002). On the individual patient level the cause of bilateral fMRI-activation is mostly a matter of uncertainty. Mistaking language-associated cortex or artificially highlighted areas for language-essential cortex, however, can have relevant impact on the surgical strategies and the postoperative outcome (Desmond and Chen, 2002; Loring et al., 2002).

To overcome the problem how to classify patients with intermediate fMRI-LI, many groups propose the use of fMRI-lateralization index thresholds between +1 and −1 to discriminate unilateral from bilateral dominant patients in fMRI. Liegeois et al. (2004) use a lateralization index of ±0.1. Springer et al. (1999), Szaflarski et al. (2002), and Sabbah et al. (2003) use ±0.2, Sabsevitz et al. (2003) ±0.25, and Adcock et al. (2003) use ±0.265. Lehericy et al. (2000) defined LI between 0.5 and 1 to represent strong, and an LI between 0.25 and 0.5 to represent weak language lateralization. However, these studies predominantly targeted on the match of fMRI and Wada-tests on the group level or on the distribution of language dominance patterns in function of various biographical factors or the side of the seizure focus. With exception of the study of Sabsevitz et al. (2003) the studies do not address the problem of language dominance prediction on the single case level.

The current study sets out to examine if the proposed thresholds actually solve the problem of bilateral fMRI-activations in clinical routine, i.e. if they allow detecting atypical language dominance in individual patients. We perform an analysis of fMRI-LI found in atypical dominant patients. The fMRI-protocol applied in this study is a semantic decision task which reliably activates frontal and temporo-parietal cortex (Fernandez et al., 2003). To