Shift-back of right into left hemisphere language dominance after control of epileptic seizures: Evidence for epilepsy driven functional cerebral organization

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Abstract

Atypical, i.e. right hemisphere language dominance is frequently observed in early onset left hemisphere epilepsies. In left mesial temporal lobe epilepsy, where eloquent cortex is not directly involved, it is a matter of debate, to which degree atypical language dominance is driven not only by morphological lesions but also by epileptic dysfunction, and whether atypical dominance is hardwired or not. Taking this as the background this study evaluated the hypothesis that epilepsy driven atypical dominancy might be reversible when seizures are successfully controlled. This was evaluated in patients with left mesial temporal lobe epilepsy, who were atypically language dominant by means of language fMRI before surgery, and became seizure free after left selective amygdalo-hippocampectomy. Three out of 53 consecutive atypically dominant patients with chronic epilepsy fulfilled these criteria. Postoperative follow-up language fMRI indicated reversal of right into left dominance in one patient going along with unexpected losses in verbal memory performance. The two other patients experienced unchanged or even enhancement of the pre-existing dominance pattern, going along with consistent postoperative performance changes in cognition. The data thus provide supporting evidence that atypical language dominance can indeed be functionally driven and moreover that in at least some patients, right hemispheric language can shift-back to the left hemisphere when the driving factor, i.e. seizures, becomes successfully controlled. The results have clinical implications for outcome prediction after brain surgery in atypically dominant patients with epilepsy. However, further research in larger groups of atypically dominant patients is required to identify the conditions under which atypical dominance becomes hardwired and when not.

Keywords: Epilepsy; Functional plasticity; Language dominance; Surgery; Seizure control; fMRI

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1. Introduction

Right hemisphere language dominance is a very rare condition in healthy subjects (∼6%) (Knecht et al., 2000; Springer et al., 1999) but is more prevalent after left hemispheric brain damage if this was acquired early in life in a time window until puberty (Rasmussen and Milner, 1977; Staudt et al., 2002). In the presence of early brain damage, atypical language dominance represents the attempt of the maturing and still functionally plastic brain to preserve or restore language function, which obviously has superior relevance in human phylo- and ontogenetic development. In patients who suffer from early onset left hemispheric epilepsy up to 40% display right hemispheric language functions to some degree (Helmstaedter et al., 1997). This in itself fascinating phenomenon gains additional interest because of the recent suggestion from clinical observations, that a shift in language dominance may not only be induced by damage of brain tissue but also by epileptic dysfunction (Helmstaedter et al., 1997; Janszky et al., 2003; Regard et al., 1994). Correlation of atypical dominance with epileptic activity and the fact that lesions alone do not suffice to explain atypical language dominance in epilepsy patients gave rise to the interesting hypothesis that atypical dominance – at least in some patients – might not be hardwired but principally reversible if epilepsy, i.e. seizures, becomes successfully controlled (Gleissner et al., 2002). Patients with left mesial hippocampal sclerosis as the sole pathology appear particularly interesting in this respect since it is remarkable that such a circumscribed structural lesion in primarily memory processing structures should cause the brain to shift language to the right hemisphere (Helmstaedter et al., 1994; Knecht, 2004). First empiric support for the back-shift hypothesis of epilepsy driven right hemisphere language to the left hemisphere was inferred indirectly from behavioural assessment (Gleissner et al., 2002; Helmstaedter et al., 2004). This hypothesis was based on the observation of a postoperative reversal of the so called suppression or crowding effect, which describes the suppression or sacrifice of originally right hemisphere functions in favour of a right hemisphere restitution of language after left hemispheric damage (Lansdell, 1969). Direct evidence for the reversal of atypical language dominance could not yet be obtained since the gold standard for language lateralization (separate intracarotid anaesthesia of the left/right hemisphere) is invasive and thus not repeatable after surgery. However, now that functional magnetic resonance imaging (fMRI) allows for reliable and repeated non-invasive assessment of language dominance, direct evaluation of the back-shift hypothesis is possible (Fernández et al., 2002). For this purpose patients were selected according to the following criteria: left mesial temporal lobe epilepsy (TLE) with hippocampal sclerosis as the sole epileptogenic pathology, left selective epilepsy surgery (amygdalo-hippocampectomy/SAH) not affecting language relevant cortex, no persisting seizures postoperatively, and significant right hemisphere language involvement before surgery as determined by preoperative fMRI.

2. Patients and methods

Only 3 of 53 patients with atypical language dominance (fMRI) fulfilled the above described selection criteria. These patients were offered payment for undergoing follow-up fMRI and neuropsychological evaluation, and they agreed to participate in the follow-up evaluation. Functional MRI as well as neuropsychological testing were routinely conducted as part of the presurgical evaluation. In two cases they were carried out a few days before the operation and one patient had surgery 2 months after the presurgical workup. Follow-up fMRI and neuropsychological evaluation were performed on the same day. Follow-up intervals were 9, 18, and 24 months in the three patients (see Table 1).

As for individual patient characteristics, patient GR suffered from epilepsy since her first year of life, starting medication when she was four (for patient description see Table 1). At the age of 41 she submitted herself to presurgical evaluation with a medically intractable epilepsy. Before, she had suffered five complex partial seizures a month with secondary generalization about six times a year. Interictally no epileptic activity was recorded. Structural MRI showed left sided hippocampal sclerosis and slight atrophy of the left temporal lobe. Handedness was ambidextrous with a dominant use of the right hand.

Patient LG suffered from meningitis with 9 months. She developed epilepsy with 19 years of age with complex partial seizures once or twice a month (cata-
Table 1
Patient characteristics and pre- and postsurgical laterality indices

<table>
<thead>
<tr>
<th>Patient</th>
<th>GR</th>
<th>LG</th>
<th>FW</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>41 years</td>
<td>38 years</td>
<td>63 years</td>
</tr>
<tr>
<td>Sex</td>
<td>Female</td>
<td>Female</td>
<td>Male</td>
</tr>
<tr>
<td>Handedness&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.67</td>
<td>−0.67</td>
<td>1</td>
</tr>
<tr>
<td>Age at epilepsy onset</td>
<td>1 year</td>
<td>19 years</td>
<td>12 years</td>
</tr>
<tr>
<td>Seizure frequency/month</td>
<td>5</td>
<td>1–2</td>
<td>7</td>
</tr>
<tr>
<td>(GTCS + CPS) before surgery</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Follow-up interval/months</td>
<td>18</td>
<td>24</td>
<td>9</td>
</tr>
<tr>
<td>Language dominance&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anterior/expressive</td>
<td>−0.26</td>
<td>+0.95</td>
<td>−0.91</td>
</tr>
<tr>
<td>Posterior/receptive</td>
<td>−0.39</td>
<td>+1.00</td>
<td>−0.53</td>
</tr>
</tbody>
</table>

<sup>a</sup> Handedness lateralization: −1 left; +1 right (oldfield handedness inventory).
<sup>b</sup> Language dominance: −1 right; +1 left.

Meninal accumulation) and secondary generalization once a year. Intercital epileptiform discharges were seen during sleep and indicative of temporomesial lobe epilepsy. The structural MRI solely showed left sided hippocampal sclerosis. When entering presurgical evaluation LG was 38 years old; handedness ambidextrous with a dominant use of the left hand.

Patient FW suffered from epilepsy since he was 12 years old. He experienced simple and complex seizures in clusters of a week once a month. At the age of 55 the first generalized tonic clonic seizure occurred. Intercital epileptiform discharges were recorded from left fronto-temporal structures with a leading temporal focus indicative of mesial temporal lobe epilepsy and consistent left sided hippocampal sclerosis as shown by MRI. MRI furthermore depicted an old posttraumatic defect in the right frontal lobe which did not turn out as epileptogenic. He underwent presurgical workup at the age of 63 and was righthanded.

Postoperatively, all three patients were seizure free (Engel Class I), and routine surface EEG recordings revealed no epileptiform discharges. However, patient FW suffered a single seizure 3 months after his operation.

Language mapping via fMRI was performed by a semantic decision task, which requires the comparison of word pairs with respect to their semantic content as to whether the words have synonymous meaning or not. To control for perceptive processes, a perceptual control task was applied in which the subjects were asked to compare two letter strings in regard to the identity of their respective characters. The amount of activation in a priori defined regions of interest (anterior frontal expressive and posterior temporoparietal receptive language area, see figure) in the left and right hemisphere was measured to calculate a laterality index ranging from −1 right dominance to +1 left dominance for both regions of interest. A detailed description of the statistical methods and the paradigm has been given before (Fernández et al., 2002).

Neuropsychological examination included assessment of intelligence, verbal/figural memory, language functions and visuo-spatial functions. Preoperative testing occurred within standard diagnostic workup. Postoperative examination comprised the same tests except for IQ which was evaluated only preoperatively. Cognitive domains were rated as impaired or changed when at least two parameters indicated statistically significant impairment (result < 1 standard deviation, S.D.) or significant change (90% reliability of change interval, RCI).

3. Results

3.1. fMRI results

Accordingly, patient GR showed a right > left hemisphere activation in both language areas before surgery, patient LG was almost complete right hemisphere dominant, and patient FW showed a bilateral dissociated expressive (right > left) and receptive (left > right) language activation pattern (see Table 1 and Fig. 1). Postoperatively, patient GR showed a change from right to complete left dominance in both the receptive and expressive language region. Patient LG remained
unchanged, and in patient FW the dissociation became more pronounced.

3.2. Neuropsychological results

The patients’ performance is shown in Table 2. Patient GR showed an intelligence in the range of a borderline deficiency. Preoperatively, in patient GR there was evidence of a suppression or crowding effect showing better verbal than nonverbal functions despite left hemisphere epilepsy. This profile was pronounced in the memory domain. Postoperatively verbal memory further declined, figural memory and visual, nonverbal functions were unchanged and improvement was seen only in some language functions. Against the background of an average intelligence, patient LG showed verbal memory impairment as it would be expected in left TLE. Postoperatively memory was unchanged but language and visuo-spatial functions significantly improved. Patient FW showed average intelligence and almost unimpaired partial functions, language functions being the exception. This patient showed postoperative decline in figural memory to a level below average.

### Table 2

<table>
<thead>
<tr>
<th></th>
<th>GR</th>
<th>LG</th>
<th>FW</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre</td>
<td>Post</td>
<td>Pre</td>
<td>Post</td>
</tr>
<tr>
<td>IQ</td>
<td>+</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Verbal memory</td>
<td>+ ↓</td>
<td>++ →</td>
<td>– →</td>
</tr>
<tr>
<td>Language functions</td>
<td>+ ↑</td>
<td>+ ↑ →</td>
<td>+ ↑ →</td>
</tr>
<tr>
<td>Figural memory</td>
<td>+++ →</td>
<td>+ →</td>
<td>– →</td>
</tr>
<tr>
<td>Visuo-spatial functions</td>
<td>++ →</td>
<td>+ ↑ →</td>
<td>– ↓</td>
</tr>
</tbody>
</table>

Cognitive domains: IQ: WAIS-R (short version); verbal memory: learning, memory, recognition; figural memory: learning, memory, recognition; language: comprehension, fluency, naming; visual spatial: mental rotation, orientation, visuo-construction. Impairment: –, unimpaired; +, mean < 1S.D.; ++, mean < 2S.D.; +++, mean < 3S.D. Performance change: →, unchanged; ↑, improvement (90%-RCI); ↓, deterioration (90%-RCI).
4. Discussion

Previous reports showed that atypical language in patients with epilepsy might not only be hardwired but also epilepsy driven. Behavioural observation in three atypical language dominant patients, who after left temporal lobe surgery showed a reversal of the so called crowding phenomenon together with unexpected losses in verbal memory, raised first evidence that language dominance may reverse. Taking these findings as a background, the present study aimed at demonstrating the possibility of reversal or reshift of atypical language dominance after epilepsy surgery via functional MRI. This was evaluated in a highly selected group of patients who were atypically language dominant in the presence of a left mesial temporal lobe epilepsy with hippocampal sclerosis and who furthermore became absolutely seizure free by selective removal of the temporomesial structures. In these patients pre- and postoperative lesional affection of language relevant prefrontal or temporo-posterior structures and thus a lesional driven shift of language to the right hemisphere could be excluded. Furthermore epilepsy as the potentially driving factor was controlled after surgery. These conditions were found in 3 of 53 preoperative patients with atypical language dominance. In one of these patients the expected postoperative reversion of atypical language dominance into clear left dominance could be demonstrated. The other two patients showed postoperatively stable or even enhanced preoperative language dominance pattern. Consistent with our previous observation the patient who showed a reversal of atypical dominance also demonstrated a suppression effect (preserved verbal and impaired figural memory) before surgery and a significant loss in verbal memory after left sided surgery as it would have been expected in a left dominant patient (Lee et al., 2002). The other two patients neither showed a preoperative suppression effect nor did they show a loss in verbal memory after surgery.

These so far are observations in single patients and evaluations in larger groups of patients must be awaited in order to study the conditions of stable versus dynamic language dominance patterns in adult patients with epilepsy and temporo-mesial epilepsy in particular. Nevertheless the findings can be taken as first evidence of the existence of a functionally driven and principally reversible atypical language dominance pattern in the adult brain. Regarding the question, why this re-shift phenomenon occurred only in patient GR, it seems important that only in this patient, epilepsy occurred at a very early age within the time window sensitive for language acquisition and hemispheric specialization for language processing (Helmstaedter et al., 1997). The other two patients with postoperatively unchanged or even enhanced atypical language dominance had comparably late onsets of epilepsy. This observation suggests genuine rather than epilepsy driven atypical language dominance in these two patients (FW, LG), and genuine atypical dominance should be less susceptible to the change of epileptic dysfunction. The fact that one of the two patients with unchanged language dominance had an old posttraumatic right frontal lesion may be taken as an additional support for the suggestion of a genuine atypical dominance in this patient (LG). Missing preoperative crowding/suppression effects indicate another difference between the patients with unchanged versus changed language dominance. Under the assumption of a genuine atypical dominance the postoperative loss in figural memory in patient FW could be interpreted as corresponding to a postoperative loss of memory as observed after surgery in the language non-dominant temporal lobe (Gleissner et al., 1998). Against our expectations derived from the work of Janszky et al. (2003) no relation between pre- or postoperative EEG and language dominance could be established. This however does not exclude our assumption of an epilepsy driven dominance shift which becomes reversed by successful seizure control. This process resembles the release of non-temporal lobe functions after successful temporal lobe surgery, which has been interpreted to result from cessation of distant effects of the epileptic focus on these structures (Helmstaedter, 2005).

What may seem wondrous in the present case is the question of why language shifts back to the left side if this is associated with the negative side effect of a verbal memory loss. As discussed earlier with regard to equipotentiality of the hemispheres for language processing (Helmstaedter et al., 1997), also in GR the left hemisphere was obviously predisposed to process language functions. Different from the condition of extensive and irreversible brain damage including structures relevant for language processing, the idea of an epilepsy driven atypical dominance pro-
vides that irradiating epileptic dysfunction or erratic neuronal input and neuronal recruitment can force the maturing and developing brain to reversibly alter its functional organization. After successful surgery the functional pressure on the left hemisphere language structures fades and the left hemisphere is in charge again, irrespective of the negative consequence for verbal memory performance. This may also explain the clinical observation that preoperatively observed atypical language dominance in temporal lobe epilepsy not always protects against loss in verbal functions after left sided surgery (Helmstaedter et al., 2004).

In conclusion, demonstration of the possibility of reversible functionally driven language dominance in principal can be seen as an important contribution to the discussion about early and late dynamics of cerebral functional organization. Although at the present stage of progress in the field our explanations must remain speculative, we hope to stimulate future research into further differentiation of the circumstances under which atypical dominance becomes functionally driven or hardwired.

References


