Research report

Inter-hemispheric language functional reorganization in low-grade glioma patients after tumour surgery

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ABSTRACT

Despite many claims of functional reorganization following tumour surgery, empirical studies that investigate changes in functional activation patterns are rare. This study investigates whether functional recovery following surgical treatment in patients with a low-grade glioma in the left hemisphere is linked to inter-hemispheric reorganization. Based on literature, we hypothesized that reorganization would induce changes in the spatial pattern of activation specifically in tumour homologue brain areas in the healthy right hemisphere. An experimental group (EG) of 14 patients with a glioma in the left hemisphere near language related brain areas, and a control group of 6 patients with a glioma in the right, non-language dominant hemisphere were scanned before and after resection. In addition, an age and gender matched second control group of 18 healthy volunteers was scanned twice. A verb generation task was used to map language related areas and a novel technique was used for data analysis. Contrary to our hypothesis, we found that functional recovery following surgery of low-grade gliomas cannot be linked to functional reorganization in language homologue brain areas in the healthy, right hemisphere. Although elevated changes in the activation pattern were found in patients after surgery, these were largest in brain areas in proximity to the surgical resection, and were very similar to the spatial pattern of the brain shift following surgery. This suggests that the apparent perilesional functional reorganization is mostly caused by the brain shift as a consequence of surgery. Perilesional functional reorganization can however not be excluded. The study suggests that language recovery after transient post-surgical language deficits involves recovery of functioning of the presurgical language system.

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1. Introduction

The assessment of long-term effects of tumour resection on brain function is important for clinical decision-making (Rutten & Ramsey, 2010). Low-grade gliomas represent a special case among the brain tumours because they grow slowly, delaying their transformation into malign, high grade gliomas to about 7–8 years (Mandonnet et al., 2003, 2008). Though this delay in malignant transformation may suit a 'wait and see' interventional approach, it is now becoming practice to perform surgery on patients with a glioma whenever possible (Duffau, 2006; Soffietti et al., 2010). Research has shown that maximal resection of the tumour increases survival of glioma patients (Sanai, Chang, & Berger, 2011). However, increased survival comes with the risk of inducing (new) neurological deficits as gliomas often grow near, or infiltrate, essential functional brain areas (eloquent areas) (Duffau & Capelle, 2004). To avoid neurological deficits, electro-cortical stimulation mapping (ESM) is now routinely used during surgery (De Witt Hamer, Robles, Zwinderman, Duffau, & Berger, 2012; Duffau, 2012). However, intra-operative ESM does not prevent the removal of normal brain tissue (Rutten & Ramsey, 2010; Yordanova, Moritz-Gasser, & Duffau, 2011). Surgery is thus bound to damage intact functional tissue surrounding the tumour, especially when the amount of resected tissue is large (Sanai, Mirzadeh, & Berger, 2008).

Surgical removal of secondary and even primary eloquent areas causes mostly transient functional language deficits immediately after surgery (Duffau et al., 2003), that are subsequently recovered post-operatively (1–3 months after surgery) (Duffau, 2012; Hamberger & Cole, 2011). It has been suggested that this recovery of surgery-induced functional impairments is caused by reorganization that compensates for the damaged functional tissue (Desmurget, Bonnetblanc, & Duffau, 2007; Duffau, 2005). Such functional reorganization is thought to occur in the healthy, right hemisphere (Crinion & Price, 2005; Voets et al., 2006; Winhuisen et al., 2005), especially in lesion homologue brain areas as has been previously suggested for the language function (Sarubbo, Le Bars, Moritz-Gasser, & Duffau, 2012).

Empirical follow-up studies that investigate functional activation patterns after surgery are rare. Previous fMRI studies have suggested that the number of activated areas may decrease compared to before surgery (Perrone-Bertolotti, Zoubrinetzky, Yvert, Le Bas, & Baciu, 2012; Roux et al., 2000), or may increase after surgery by involving lesion homologue areas in the healthy hemisphere (Bonelli et al., 2012; Krainik et al., 2004; Sarubbo et al., 2012; Shinoura et al., 2006). At this point it is not clear whether contralesional recruitment is typical in patients, nor whether it benefits language function (Bonelli et al., 2012). Importantly, since most of the studies that stress recruitment of lesion homologue areas in the healthy hemisphere are case reports, the implication of these results for tumour surgery in general is rather limited (Perrone-Bertolotti et al., 2012; Sarubbo et al., 2012). Studies with larger cohorts can shed more light on the topic.

A major difficulty with investigating the effects of tumour resection on brain function in individual patients is that many factors can confound fMRI measures of functional reorganization. One possible confounding factor is represented by the whole brain amplitude change between the scanning sessions. By whole brain change we mean that all amplitudes of Blood Oxygen Level Dependent (BOLD) responses are scaled with a similar percentage across the entire brain from one scanning session to the other (Raemaekers, du Plessis, Ramsey, Weusten, & Vink, 2012). The whole brain amplitude of BOLD responses have been shown to fluctuate considerably in healthy subjects (Birn, Diamond, Smith, & Bandettini, 2006; Raemaekers et al., 2007; Ungerleider, Doyon, & Karni, 2002). As of yet, the cause of such fluctuations is not clear and is still an important topic of investigation since they increase variance of activation within individuals, but factors such as task compliance and mental effort have been proposed (Lohmann, Deppe, Jansen, Schwindt, & Knecht, 2004; Wexler et al., 1997). Whole brain changes in amplitudes between measurements therefore do not necessarily imply functional reorganization of the brain. Importantly, whole brain amplitude fluctuations leave the spatial pattern of activation across regions more or less intact since all regions are affected equally. The spatial pattern of activation is of interest here because functional reorganisation is expected to affect the distribution of activation across brain areas, hence the pattern of activation. Spatial pattern analyses have barely been applied to studies on functional reorganisation after tumour surgery, but they could elucidate the nature of changes in brain activity. One confound in spatial pattern analyses in this context is that activation patterns are also sensitive to changes in brain structure. Tumour resection invariably affects structure in that the remaining tissue readjusts to tissue removal and leads to brain deformation or the so-called brain shift. These deformations are the result of the release of pressure originating from the build-up of tumour tissue, causing remaining tissue to bounce back to its original position before the existence of the tumour. This causes anatomical misalignment between the scanning sessions. Brain shift of a magnitude of up to 20 mm has been reported (Hartkens et al., 2003; Hill et al., 1998; Khan, Mewes, Gross, & Skrinjar, 2008), and in some studies has also been shown to affect alignment of the healthy hemisphere (Miyagi, Shima, & Sasaki, 2007).

The present study was conducted to address some of the issues discussed above. We investigate whether patients with an LGG in the left hemisphere show inter-hemispheric reorganization following surgical treatment while performing a verb generation task. Importantly, most of these patients experienced a post-surgical transient deficit, indicating that the language system was perturbed due to the resection. We focus on the language-task induced activation pattern in the healthy, right hemisphere which we expect to display elevated involvement, notably within homologue language areas (Bonelli et al., 2012; Krainik et al., 2004; Sarubbo et al., 2012; Shinoura et al., 2006). For this purpose we scanned a group of 14 patients with a glioma in the left hemisphere before and after resection. For comparison, we scanned a group of 6 patients with a glioma in the right hemisphere before and after resection, and an age and gender matched control group of 18 healthy volunteers (also scanned twice). For data analysis we use a novel technique that discriminates

between activation changes due to global effects and changes in the pattern of activation (Raemaekers et al., 2012).

2. Materials and methods

2.1. Background

The purpose of this analysis was to estimate functional reorganization induced by surgery in the healthy hemisphere of glioma patients. With functional reorganization we specifically mean differences in BOLD signal before and after surgery that affect the spatial pattern of activation. The procedure for quantifying the amount of change in the activation pattern used here is based on a method developed by Raemaekers and colleagues (Raemaekers et al., 2012) for estimating test-retest variability of fMRI activation.

The method discriminates test-retest changes in *whole brain* BOLD signal and changes in the *spatial pattern* of the BOLD signal. Whole brain changes in the amplitude of the spatial pattern of activation occur when the amplitudes of BOLD responses are affected to a similar extent across the entire brain, changing the amplitude of activation in all voxels by the same percentage. This type of variability could be caused by differences in task compliance or in effort which may be considered secondary factors when looking for true surgical effects on functional organization. Surgery is expected to affect the spatial pattern of activation. Changes in the spatial pattern of activation occur when the relative proportional activation of one voxel to the next changes after taking whole brain changes in the amplitude of activation into account. This type of variability is expected when the functional architecture of the brain changes as a result of surgical treatment. However, this type of variability may also be the result of brain shift which causes anatomical misalignment between the scanning sessions. Previous results showed that in healthy subjects the main source of between session variability in BOLD signal is due to whole brain changes in amplitudes. Changes in the spatial activation pattern in healthy subjects could all be explained by effects of partial voluming or geometric distortions induced by magnetic and radio-frequency field inhomogeneities (Raemaekers et al., 2012).

Between-session changes in the underlying BOLD signal were assessed by analysing properties of scatter plots of regressor coefficients (b-values) (see Fig. 1 for illustration). These plots are analysed for each subject individually. For each subject the b-values of the first scanning session (on the x-axis) are plotted against the b-values of the second scanning session (on the y-axis). Every data point in the pattern thus represents a single voxel in the brain. The error bars represent the standard deviation of the regressor coefficients during the first (horizontal bars) and second (vertical bars) session.

A straight line is fitted through the data points that can be described by the formula $y = ax + b$, where a is the slope and b is the intercept. *Whole brain* changes in the amplitudes of BOLD responses between sessions cause the slope to deviate from 1 (which is equal to 45°).

Two important measures that can be extracted from the scatterplots are PAT_{shared} and $PAT_{difference}$. PAT_{shared} is the standard deviation of the data points (expressed in effect
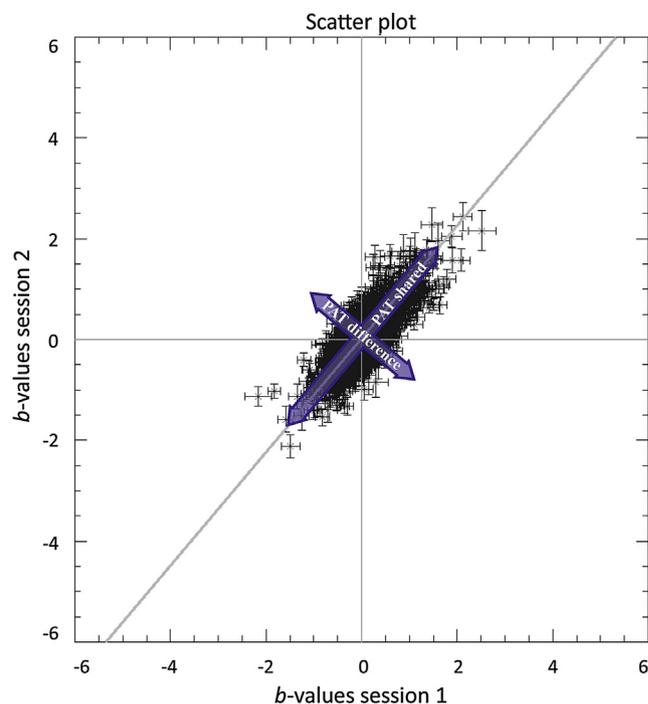
Fig. 1 – The regressor coefficients (*b*-values) scatter plot of one of the healthy subjects. Each dot (represented by a *cross*) represents the *b*-value in the first (on the *x*-axis) and second scanning session (on the *y*-axis). The error bars show the standard deviation of the *b*-values in the first (horizontal bars) and second (vertical bars) scanning session. The straight line fitted through the data points is given in *grey* and has a slope of 48.35°. $PAT_{difference}$ represents the standardized distance in effect sizes of the data points towards the fitted line. PAT_{shared} represents the standardized distance in effect sizes of the data points towards the origin along the fitted line.

sizes) from the origin of the plot along the fitted line (after they are projected orthogonally onto the fitted line). PAT_{shared} represents the amount of activation pattern (PAT) that is shared between the two scanning sessions, before and after surgery. $PAT_{difference}$ is the standard deviation of the data points (expressed in effect sizes) from the fitted line. $PAT_{difference}$ represents the amount of changes in the *spatial pattern* of activation between the two scanning sessions before and after surgery. PAT_{shared} and $PAT_{difference}$ can be computed for any predetermined region of interest (ROI). PAT_{shared} and $PAT_{difference}$ were computed after masking out the surgical resection of the tumour. The mask was manually reconstructed by filling in the surgical resection cavity. The amount of changes in the *spatial pattern* of activation ($PAT_{difference}$) in a brain area is previously found to proportionally increase with the amount of activation that is shared between sessions (PAT_{shared}) in that brain area (Raemaekers et al., 2012). A surgery-induced *excess* change in the *spatial pattern* of activation between scanning sessions can thus only be adequately investigated by examining between area and between subjects differences in the *ratio* between $PAT_{difference}$ and PAT_{shared}. In this study we investigate differences in the ratio

between $PAT_{difference}$ and PAT_{shared} between the tumour homologue and non-homologue brain areas in the healthy hemisphere within patients, and between patients and healthy subjects. By this we address the question whether there is functional reorganization of language related brain areas following tumour surgery, and whether these changes specifically affect the functional architecture of the tumour homologue brain areas in the healthy right hemisphere.

2.2.   Participants

Eighteen healthy subjects (9 females and 9 males, M age = 39.7 years, SD = 11.4), and twenty consecutive patients with a primary brain tumour (low-grade glioma) referred for awake surgical treatment to the St. Elisabeth Hospital (Tilburg, Netherlands) were included in this study. We included suspected low-grade or anaplastic glioma (grade I—III according to WHO) that were radiologically confined to one hemisphere. The healthy subjects had no neurological deficits on clinical examination while all patients had experienced epileptic seizures before admission for which they were treated with antiepileptic drugs. All subjects were strongly right handed according to the Edinburgh Handedness inventory (Oldfield, 1971) (healthy controls M = .85, SD = .15, patients M = .94, SD = .12). Details on the patients, including the tumour location and volume of resection, are given in Table 1. Anatomical images before and after surgery for all patients are given in Supplement 1. None of the subjects had previous experience with fMRI or with the tasks performed outside or in the scanner. Subjects were scanned and tested at the University Medical Center Utrecht (UMC Utrecht, The Netherlands) after giving informed consent approved by the medical ethics committee for research in humans of the UMC in accordance with the Declaration of Helsinki of 2008. The test-retest

scanning and neuropsychological testing interval was on average 7 weeks (M = 48 days, SD = 21) for the healthy subjects, and 20 weeks (M = 151 days, SD = 47) for the patients (M = 25 days, SD = 21 from first scanning session to surgery; M = 126 days, SD = 48 from surgery to second scanning session).

2.3.   Surgical procedure

All patients underwent surgery under local anaesthesia to allow for cortical and subcortical electrical stimulation of critical sensorimotor and language structures. Tumour borders were identified with the aid of a surgical guidance system (Stealth S7, Medtronic) that included T1 weighted images with gadolinium, FLAIR images and relevant subcortical fibre tracts from DTI (corticospinal tract, inferior fronto-occipital fasciculus, arcuate fasciculus and/or optic radiation). The bone flap exposed the tumour and part of the surrounding normal brain. Tumour resection was performed according to the principles of sulcal-to-sulcal surgery whereby the extent of resection was determined by the results of electro-cortical stimulation (i.e., according to functional boundaries), patient performance and surgical judgement that all FLAIR abnormalities had been removed (acknowledging the limitations of the surgical guidance systems due to brain shift). Electrical stimulation was performed with a bipolar probe with 5 mm distance between the tips (ISIS, Inomed). A biphasic current was applied for a maximum duration of 4 sec (frequency 60 Hz, pulse duration .5—1 msec, current 2—8 mA). During (sub)cortical stimulation as well as during tumour resection patients performed motor and language tasks and were continuously monitored by a neuropsychologist. Incidentally, other tasks were used (e.g., counting and subtracting).

Table 1 — Patients' clinical and pathological details.

Patient's			Tumour's			
Code	Age	Sex	Histology[a]	Hemisphere	Lobe	Volume[b]
1	42	Male	A2	Right	Frontal	3.78
2	36	Male	A2	Right	Fronto-temporal	18.50
3	47	Male	A2	Right	Frontal	32.19
4	31	Female	O2	Right	Frontal	4.10
5	37	Female	OA2	Right	Frontal	1.58
6	48	Female	A4	Right	Parietal	15.23
7	36	Male	O2/3	Left	Fronto-parietal	4.22
8	39	Male	O2/3	Left	Frontal	39.36
9	55	Male	O2	Left	Temporo-occipital	14.02
10	39	Male	A2	Left	Fronto-temporal	56.58
11	31	Male	O2	Left	Frontal	9.47
12	44	Male	O2	Left	Frontal	7.55
13	56	Male	O2	Left	Temporo-occipital	11.52
14	43	Male	O2/3	Left	Temporo-parietal	23.49
15	34	Male	O2	Left	Temporal	19.58
16	32	Female	O2	Left	Frontal	31.55
17	51	Female	O2	Left	Frontal	18.37
18	26	Female	A2/3	Left	Parietal	13.63
19	51	Female	O2	Left	Frontal	27.52
20	52	Female	O2	Left	Temporal	4.74

[a] WHO classification: A = astrocytoma; O = oligodendroglioma; OA = oligoastrocytoma; number = WHO grade.
[b] Resected volume as measured from the post-surgical structural image; units in cm^3.

While the surgical procedure minimizes chances on the impairment of language function, it does not automatically imply that fMRI-activated language voxels were not removed. However, detailed assessment of the number of removed language voxels is complicated by brain shift between before and after surgery.

2.4. Clinical examinations

Clinical examinations were routinely performed in all patients about 1 month before surgery, during surgery, immediately after surgery, and approximately 4 months after surgery by the treating neurosurgeon. Subsequent language or other neurological deficits were recorded in patient files. Special attention was paid to any kind of dysphasia present in the immediate postoperative period (first week during hospital stay), as well as to the course of recovery over the following weeks and months. Symptoms of dysphasia included language disturbances such as difficulty in understanding spoken language or speaking meaningful sentences, remembering or using correct words, and difficulty in naming, reading or writing. A description of the clinical examinations is given in Table 2. Most of the patients showed no to slight language deficits before surgery. Patients with a glioma in the left hemisphere (n = 14) were awake operated for monitoring of (sub)cortical language functions. These patients showed a gradual or occasional worsening of language during resection and responded positively to electrical stimulation (see section 2.3) during surgery. Most of these patients had as well an acute worsening of language immediately after surgery, and a full or partial recovery to pre-surgical levels at approximately 4

months after surgery. Patients with a glioma in the right hemisphere (n = 6) were awake operated for monitoring of (sub)cortical sensorimotor functions (not reported here). As expected, these patients showed no worsening of language during resection and showed no worsening of language immediately or 4 months after surgery.

We consider therefore the patients with a glioma in the left hemisphere as the experimental group (EG) and the patients with a glioma in the right hemisphere as the control group (CG I). Healthy subjects represent then another control group (CG II).

After each scanning session, before and after surgery, patients were administered by trained neuropsychologist the Dutch version of the National Adult Reading test (Nelson & O'Connell, 1978; Schmand, Bakker, Saan, & Louman, 1991), Ravens Matrices test, Trial Making test (part A and part B), and the Digit Span test (Lezak, Howieson, & Loring, 2004). Description of the neuropsychological tests and procedures is found in Table 3. The neuropsychological task performance data were analysed to check whether variations in the spatial pattern of fMRI activation were related to variations in cognitive performance. For each patient, raw scores on each cognitive test were first converted to standardized scores (z-scores) using age-based or age and education-based norms. Z-scores were than averaged over all cognitive tests creating a composite cognitive score indicating Global Neuropsychological Functioning (GNF) of patients (Ownsworth, Dwan, Chambers, Walker, & Shum, 2014). The GNF scores before surgery were then subtracted to GNF scores after surgery. A positive score means a better neuropsychological functioning of patients after surgery.

Table 2 – Patients' language related clinical examinations.

Code	Preoperative deficit[a]	Perioperative deficit[b]	Postoperative deficit[c]	Surgery in language areas	Postoperative recovery[d]	Neuro psychological tests[e]
1	No	No	No	No	No	Yes
2	No	No	No	No	No	No
3	No	No	No	No	No	Yes
4	No	No	No	No	No	Yes
5	No	No	No	No	No	Yes
6	No	No	No	No	No	Yes
7	Yes	Yes	Yes	Yes	Partial	Yes
8	No	Yes	Yes	Yes	Yes	Yes
9	Slight	Yes	Yes	Yes	Yes	Yes
10	No	Yes	Yes	Yes	Yes	Yes
11	No	Yes	No	Probable	No	Yes
12	No	Yes	Yes	Yes	Yes	Yes
13	Yes	Yes	Yes	Yes	Partial	No
14	No	Yes	Yes	Yes	Yes	Yes
15	Slight	Yes	Yes	Yes	Yes	No
16	No	Yes	No	Probable	No	Yes
17	No	No	Yes	Yes	Yes	Yes
18	No	No	No	No	No	No
19	No	Yes	No	Probable	No	No
20	Slight	Yes	Yes	Yes	Yes	Yes

[a] One month before surgery.
[b] Due to resection or electrical stimulation.
[c] Immediately after surgery.
[d] Four months after surgery.
[e] One month before and four months after surgery.

Table 3 – Contents of neuropsychological assessments.

Neuropsychological tests	Content
National Adult Reading Test (Dutch version)	The National Adult Reading Test (NART) is a verbal neuropsychological task that assesses premorbid intelligence level. It requires reading of 50 irregular words. The score is the number of correctly pronounced words. The NART score is transposed into an Intelligent Quotient (IQ) score.
Raven's Matrices	Raven's Advanced Progressive Matrices is a nonverbal neuropsychological task that assesses abstract reasoning (general intelligence). The short version of this test presented to our patients is made of 12 multiple choice questions listed in order of difficulty. In each test item, the subject is asked to identify the missing element that completes a pattern, presented in the form of a 3×3 matrix in black ink on a white background.
Trial Making A and B	The Trail Making Test is a nonverbal neuropsychological task that consists of two parts, A and B. Part A assesses cognitive processing speed, while part B assesses executive functioning. The test taker is instructed to connect a set of 25 dots as fast as possible while still maintaining accuracy. The test taker has to connect in part A, in sequential order, the dots consisting of numbers (1, 2, 3, etc.), and in part B, in alternate order, the dots consisting of numbers and letters (1, A, 2, B, etc.). The time taken to complete the test is the primary performance metric. The test administrator corrects the test taker in case of errors, which are assumed be reflected in the completion time.
Digit Span	The Digit span task is a verbal neuropsychological task used to measure the attention span (forward version) and working memory (backward version), which are involved in many everyday tasks, from remembering a telephone number to understanding long and difficult sentences. Participants are presented with an increasing series of digits (e.g., '8, 3, 4') every two trials. Participants must immediately repeat the digits in the given order in the forward version, and in reverse order in the backward version. The score of what a participant can remember in the forward and in the backward version is the participants' digit span.

2.5. Functional MRI task

The fMRI experimental design was the same for both scanning sessions. Participants were informed about the experimental procedure, and briefly practiced the task with the aid of a laptop before the scanning session. We used a PC, a rear projection screen and a video projector system for stimulus presentation. Visual stimuli were projected in white on a dark background. The screen was black in the first 7 sec of the experiment. The verb generation task (Ramsey, Sommer, Rutten, & Kahn, 2001; Rutten, Ramsey, van Rijen, & van Veelen, 2002; van Veelen et al., 2011) consists of five language blocks (27 sec) which are alternated with non-language control blocks (27 sec). Blocks were time locked to the fMRI scans. During the control blocks subjects had to fixate on the centre of the screen and make a button-press when an asterisk appeared (one to three per block), to verify compliance with the task. During the language blocks a noun was presented on the screen every 3 sec and subjects had to subvocally (covert articulation) generate a related verb for the presented noun (e.g., coffee → drink). There was a 2 sec period between blocks where the screen was black. Four different sets of nouns were used, one for each of the practice and scanning sessions, to prevent bias from learning effects. The different sets of nouns were matched on linguistic variables.

2.6. Functional MRI acquisition

All images were obtained with a whole body 3.0 Tesla (3T) Philips Achieva MRI scanner (Philips Medical Systems, Best, The Netherlands). The participant's head was held in place with padding. Heartbeat was recorded using a pulse-oximeter placed on the left index finger. Respiration was measured with a pneumatic belt positioned at the level of the abdomen (Birn et al., 2006).

First, a T1 weighted structural image of the whole brain in sagittal orientation was acquired for anatomical reference (3D FFE pulse sequence; acquisition parameters: TR 8.4 msec, TE 3.8 msec; FOV $288 \times 288 \times 175$ mm; voxel size 1 mm isotropic; SENSE p-reduction/s-reduction 2/1.3; flip-angle 8°; 175 slices; scan duration = 265.8 sec).

For functional scans, 3D-PRESTO (Neggers, Hermans, & Ramsey, 2008) was used covering the whole brain with the following parameters: TR 22.5 msec; effective TE 32.4 msec; FOV $256 \times 224 \times 160$ mm, voxel size 4 mm isotropic; matrix $64 \times 56 \times 40$; SENSE p-reduction/s-reduction 1.8/2; flip-angle 10°; scan duration .6075 sec (for the whole volume). 486 functional images were acquired in sagittal orientation with a foot-head frequency encoding direction.

Finally, a PRESTO scan with the same field of view and scan parameters, but with a flip-angle of 27° (called FA27), was acquired in .72 sec and used in the image coregistration routine (see section 2.7).

2.7. Functional MRI pre-processing and analysis

The first 10 scans (7 sec) were discarded from the analysis. Functional images of both scanning sessions were corrected for motion (realigned) and resliced to the Fa27 of the first scanning session using SPM5 (http://www.fil.ion.ucl.ac.uk/

spm/). Then, custom Matlab scripts were used (Aztec, http://www.ni-utrecht.nl/downloads/aztec) for correction of cardio-respiratory artefacts. The correction method used is described in detail in the study of van Buuren and colleagues (van Buuren et al., 2009). After these corrections, the functional images were high-pass filtered (Gaussian-weighted least squares straight-line fitting, with sigma = 29 sec) in FSL, version 5.92 (http://www.fmrib.ox.ac.uk/fsl/) (Smith et al., 2004). Finally, the functional images were skull stripped (Smith, 2002) and normalized by a single scaling factor (grand mean scaling) in FSL. No spatial smoothing was performed on the functional images as this is inappropriate for clinical decision-making (Rutten, van Rijen, van Veelen, & Ramsey, 1999).

The pre-processed functional data were analysed using a whole brain univariate General Linear Model (GLM) (FEAT in FSL). Time series statistical analysis was carried out using FILM, with pre-whitening to account for local autocorrelation (Woolrich, Ripley, Brady, & Smith, 2001). The haemodynamic response function was modelled using a boxcar convolved with a double gamma variate function and its temporal derivative. To correct for head motion, the six realignment parameters were included in the design matrix of the tasks as regressors of no interest. These analyses resulted in whole brain individual b-maps (for each of the two sessions) containing the regression coefficients for each voxel, and the corresponding standard deviations of the b-values.

The analysis was supplemented with the lateralization index (LI) as alternative approach to investigate signs of reorganization. LI was calculated in bilateral cortical segments known as Broca's area (i.e., pars opercularis, triangularis, and orbitalis) and in frontal lobes for each of the participants and scanning sessions. A threshold set to include the most active 5% of the voxels in the left (L) and right (R) hemisphere was used on the functional images (Kristo et al., 2014). LI was then defined as (L − R)/(L + R) and ranged therefore from −1 (right lateralized) to 1 (left lateralized) (Rutten et al., 2002).

2.8. Segmentation of cortical areas

The FreeSurfer software package (Dale, Fischl, & Sereno, 1999; Fischl, Sereno, & Dale, 1999) was used for generating surface reconstructions of the cortex for every participant. Cortical surface reconstructions for healthy subjects were based on a (non-normalized) T1 weighted image that was the average over the two scanning sessions, while cortical surface reconstructions for patients were based on the T1 weighted image acquired before surgery. An automatic surface based parcellation algorithm segmented the different cortical areas (Desikan et al., 2006; Fischl et al., 1999), and the surface based segments were subsequently converted back to the volume of the anatomical scan. See Fig. 2 for reference of the different cortical segments (ROIs) that were generated. Cortical reconstructions of all patients are given in Supplement 2. Segments only included voxels in grey matter. The resulting volumes were then co-registered to the FA27 of the first scanning session with nearest neighbour interpolation by using the (mean) T1 image as source.

3. Results

3.1. Changes in the spatial pattern of activation

Changes in the spatial pattern of activation were investigated by analysing $PAT_{difference}$ and PAT_{shared}, for different ROIs following a previous study (Raemaekers et al., 2012).

3.1.1. $PAT_{difference}$ and PAT_{shared}

The amounts of $PAT_{difference}$ and PAT_{shared} for different brain areas, brain hemispheres, and groups are given in Fig. 3. It can be seen that in all groups activity in the left hemisphere (indicated by PAT-shared) was higher compared to the right, specifically in the language regions (ROIs shown in Fig. 2). A repeated measures GLM was used to investigate differences in $PAT_{difference}$ and PAT_{shared} (2 measures) between brain areas (35 layers), between the left and right hemispheres (2 layers), and between the three different groups (between subjects factor). Results for PAT_{shared} did not show a significant main effect of group [$F_{(2,35)}$ = .134; p = .875], group × hemisphere interaction [$F_{(2,35)}$ = 1.497; p = .238], group × area interaction [$F_{(68,1190)}$ = .793; p = .888], or group × hemisphere × area interaction [$F_{(68,1190)}$ = 1.242; p = .093]. These results indicate
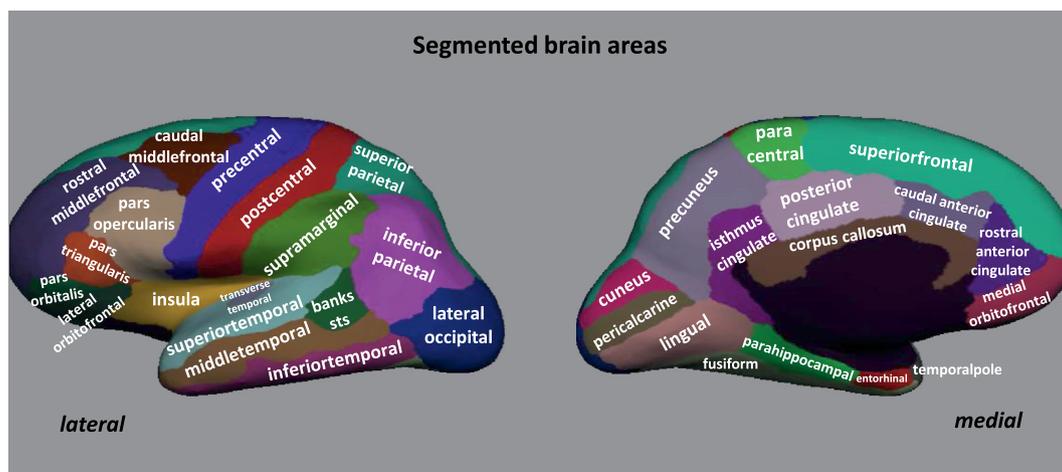
Fig. 2 – The different segmented brain areas projected on an inflated cortical surface for one of the healthy subjects. The image shows the lateral and medial surfaces of the left hemisphere.
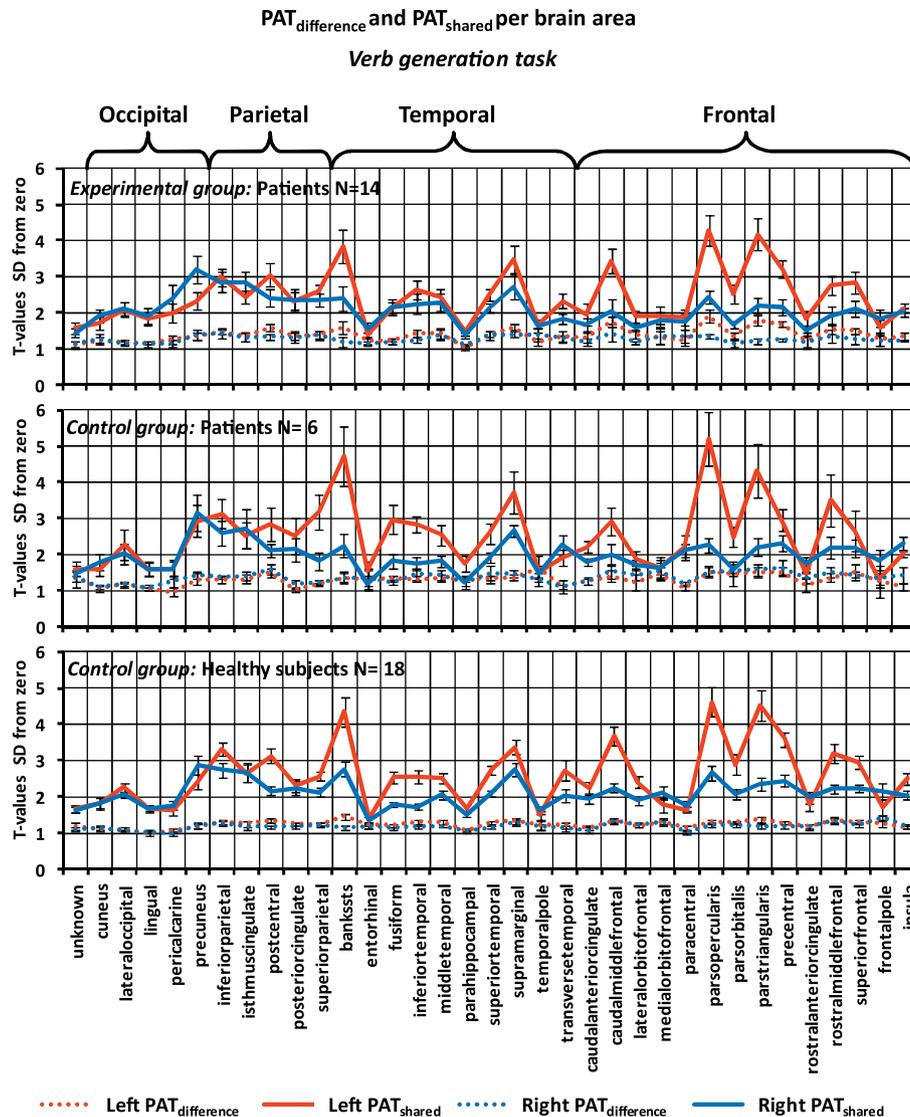
Fig. 3 – The mean estimates of PAT_{difference} and PAT_{shared} for different brain areas during the verb generation task for patients with an LGG in the left (experimental group) and right hemisphere (control group), and healthy subjects (control group). *Interrupted lines* represent PAT_{difference} and *continuous lines* represent PAT_{shared}. *Red lines* represent the results from the left hemisphere and *blue lines* represent the results from the right hemisphere. Error bars show the standard error of the mean.

that A) patients show the same activation pattern regardless of the neurological worsening during and immediately after surgery, and B) patients and healthy subjects show the same activation pattern regardless of the surgery. The highest value of PAT_{shared} was observed in known language related areas in the left hemisphere, confirming that all subjects included in this experiment (experimental and control groups) performed the verb generation task properly. These areas were the pars opercularis and triangularis (Broca's area), and the banks of the superior temporal sulcus (Wernicke's area) as shown in Fig. 3. Functional MRI maps of one subject for each scanning session and group are given as an example in Supplement 3, where conventional Z-thresholding is used. For PAT_{difference} there was a significant group × hemisphere interaction [$F_{(2,35)}$ = 3.522; p = .040] and group × area interaction [$F_{(68,1190)}$ = 1.530; p = .004]. The group × hemisphere × area

interaction was just shy of significance [$F_{(68,1190)}$ = 1.303; p = .053] and there was no main effect of group [$F_{(2,35)}$ = 1.463; p = .245]. These results indicate that there are differences in the amount of pattern variation between patients and control subjects, and that these differences are present in specific brain areas.

3.1.2. PAT_{difference} and PAT_{shared} relationship in contratumoural homologue areas

We further investigated whether the differences in the amount of PAT_{difference} found between patients and control subjects was due to an increase in variability in functional homologue brain areas in the healthy, right hemisphere of patients with an LGG in the left hemisphere as has been previously suggested (Perrone-Bertolotti et al., 2012; Sarubbo, Le Bars, Moritz-Gasser, & Duffau, 2012). For this purpose, the

ratio between $PAT_{difference}$ and PAT_{shared} for different brain areas was taken into account as $PAT_{difference}$ is known to proportionally increase with an increase in PAT_{shared} (Raemaekers et al., 2012).

For patients, ROIs from the segmentation were regrouped to form four ROI clusters that encompassed: 1) ROIs affected by the tumour (tumour-related); 2) ROIs in the tumoural hemisphere but unaffected by the tumour (non tumour); 3) ROIs in the healthy hemisphere mirroring the ROIs affected by the tumour (tumour homologue); 4) ROIs in the healthy hemisphere mirroring the ROIs unaffected by the tumour (non-tumour homologue). Note that the tumour itself was not included in the ROIs, so that the tumour-related ROIs represent intact functional tissue in brain regions affected by the tumour. While we are looking for effects in ROIs of the healthy hemisphere, ROIs of the tumoural hemisphere are included in the analysis for reference purposes. For healthy subjects, a single ROI was generated that was the combination of all ROIs. PAT_{shared} and $PAT_{difference}$ were computed for these newly defined ROIs and were plotted against each other for all patients and healthy subjects in Fig. 4. To test for differences in pattern variation (changes in the ratio between $PAT_{difference}$ and PAT_{shared}) between different ROIs and groups; A) a straight line was fitted through the data points of the healthy subjects (CG II) for reference purposes, and B) the amount of pattern variation was defined by the minimum distance of each single data point from the fitted line.

A repeated measures GLM was used to investigate differences in distance from the fitted line for the four ROIs (4 layers) between the two patient groups, the EG and CG I (between subject factor). There was a main effect of ROI [$F_{(3,54)} = 12.079$; $p < .001$], indicating that there was a difference between the areas in the amount of pattern variation. Post-hoc analysis revealed that this effect was almost entirely caused by a larger variability in tumour ROIs compared to the other ROIs [$F_{(1,18)} = 16.046$; $p = .001$], while there was no difference between the tumour homologue and non-tumour homologue areas [$F_{(1,18)} = .906$; $p = .354$]. In addition, the intercept was significant [$F_{(1,18)} = 11.089$; $p = .004$] which means that patients had on average larger pattern variation in all ROI's than control subjects. The ROI × group contrast was however not significant [$F_{(3,54)} = .144$; $p = .933$] as was the main effect of group [$F_{(1,18)} = .051$; $p = .824$], which indicates that there were no differences between patients with a tumour in the left and in the right hemisphere. The amount of pattern variation was thus unrelated to functional impairment following surgery. The changes in the activation pattern found in patients were specific to tumour-related ROIs, and were not present in the other ROIs.

To check whether increased pattern variation in contra-tumoural areas was not found due to possible absence of reorganization in patients where no recovery after surgery was observed, we repeated the analysis but including only patients with a tumour in the left hemisphere, and using presence or absence of functional recovery as between subjects factor (see Table 2). Significant main effects of ROI were again observed. There was however no indication that patients with functional recovery ($n = 10$) had increased pattern variation in tumour homologue brain areas (as compared to non-tumour homologue areas) compared to patients without functional recovery ($n = 4$) [$F_{(1,12)} = .113$; $p = .743$].

To check whether pattern variation was related to variations of change in cognitive performance, we repeated the GLM analysis using the GNF subtraction results as a covariate to the amount of pattern variation, i.e., to the minimum distance of patients' single data points from the line fitted on data
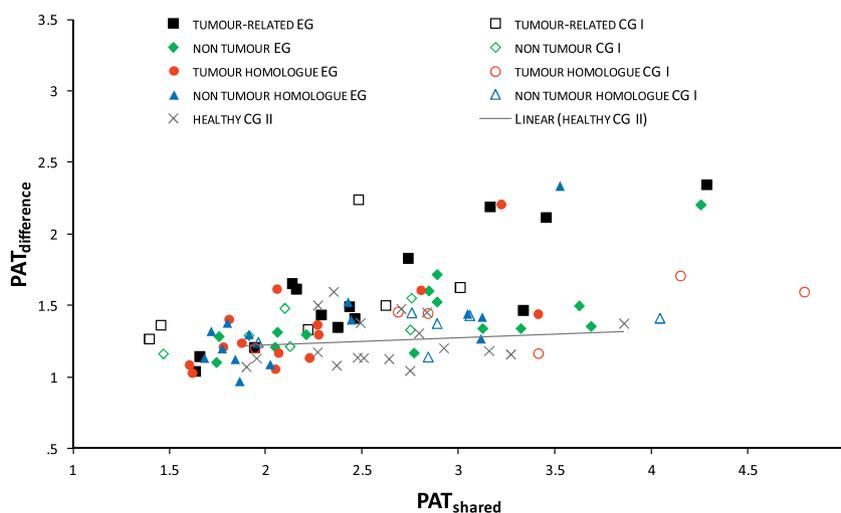
Fig. 4 — The mean estimate of $PAT_{difference}$ to PAT_{shared} ratio for all patients and healthy subjects. For patients, the mean estimates for a) tumour-related ROIs are represented by *filled black squares* for the experimental group (EG) and by *empty black squares* for the control group I (CG I); b) non-tumour ROIs are represented by *filled green diamonds* for the EG and by *empty green diamonds* for the CG I; c) tumour homologue ROIs are represented by *filled red circles* for the EG and by *empty red circles* for the CG I; d) non-tumour homologue ROIs are represented by *filled blue triangles* for the EG and by *empty blue triangles* for the CG I. The mean estimates for healthy subjects are calculated for a single ROI including all brain areas, represented by *grey crosses*, and linearly fitted for reference purposes with a *grey line*.

points of healthy volunteers (CGII). Results however showed that pattern variation was unrelated to change in cognitive functioning as measured with neuropsychological testing [$F_{(3,10)} = .045$; $p = .987$].

To check whether LI would show signs of the presence of reorganization, we performed a paired samples t-test on the lateralization indices of the patient group (EG) before and after surgery. The difference between the sessions was however not significant, whether the LI was based on Broca's area [ΔLI $= .108$; $t_{(1,13)} = 1.912$; $p = .078$], or the frontal lobes [ΔLI $= .109$; $t_{(1,13)} = 1.691$; $p = .115$]. We then performed a correlation analysis to see whether changes in GNF predicted changes in LI, but found non-significant results for Broca's area LI [$r(9) = -.280$, $p = .433$], and for frontal lobes LI [$r(9) = .043$, $p = .907$]. We therefore conclude that the LI technique did not show any signs of reorganization.

3.1.3. Brain shift

Our results suggest that changes in the activation pattern in both the EG and the CG 1 were present only in the brain hemisphere where surgery was performed. Although such increase in pattern variation could indicate functional reorganization in brain areas next to the tumour, it may also be caused by resettling of brain tissue (shift) that usually happens after the surgical resection. Because we used a linear (rigid) registration method to align the functional images before and after surgery, we have not accounted for the brain shift effect. The brain shift should in principle be larger in brain areas close to the surgical resection (where most of the resettling takes place) as compared to brain areas located far from the resection. In other words, the ratio of PAT$_{difference}$ and PAT$_{shared}$ would be larger in brain areas close to the surgical resection. To investigate this, the surgical resection was manually segmented and the resulting segment was circularly dilated fifteen times in steps of one voxel. The addition to the segment after each dilatation step was stored as a separate ROI. This resulted in fifteen ROIs that represented functional

tissue at increasing distance from the surgical resection (0–6 cm). The ratio of PAT$_{difference}$ and PAT$_{shared}$ was calculated for all 15 ROIs and for all patients. Based on the same analysis as just described, the between-session changes in the grey-white matter intensity of the anatomical (T1) image with distance to the surgical resection has been added to the plot for reference. Because of scaling differences, the values of the anatomical variability were normalized to the values of the functional variability. Results indicate that the ratio of PAT$_{difference}$ and PATshared decreases with distance to the surgical resection. The anatomical variability shows a similar decrease with distance to the surgical resection. The average correlation (calculated per individual patient) between the functional and anatomical variability was .60 ($\pm$.08). From the different functions fitted, a power function fitted best the functional [$R^2 = .966$; $t_{(1,13)} = -9.27$; $p < .001$] and anatomical variability [$R^2 = .854$; $t_{(1,13)} = -8.72$; $p < .001$] shown in Fig. 5. These results suggest that at least a large portion of the larger changes in the spatial pattern of activation found in patients in brain areas next to the tumour could be caused by the anatomical misalignment between the scanning sessions, which is caused by the brain shift following surgery.

3.2. Whole brain changes in BOLD amplitude

Whole brain changes in the underlying BOLD amplitudes were estimated separately, as it is known that these changes represent the main source of between session differences in BOLD signal in healthy subjects (Raemaekers et al., 2012). Whole brain changes were investigated by estimating the slope of the straight line fits on the scatter plots of the task-related b-values of all grey matter voxels, where an angle of 45° signifies no change in whole brain amplitude. The angles of the straight line fits are given in Fig. 6. For most of the patients and healthy subjects the angles of the straight line fits were different from 45°, meaning that global changes in underlying BOLD amplitudes did frequently occur. There were no
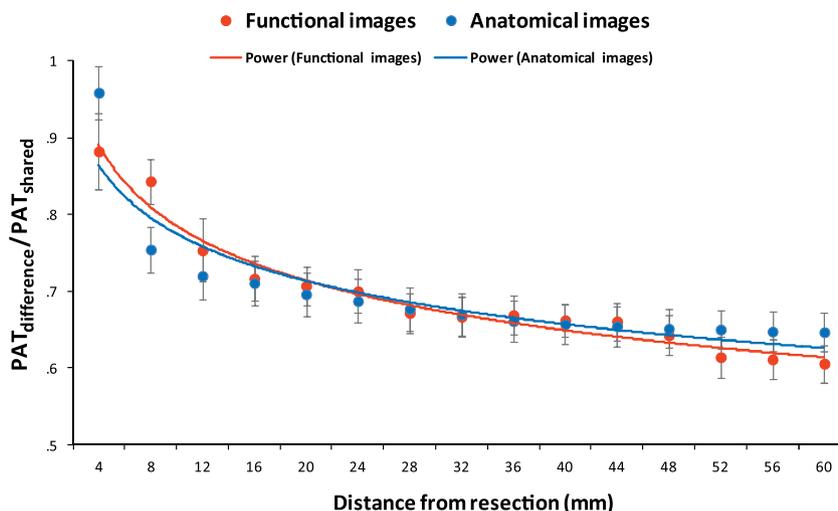
Fig. 5 — The proportion of PAT$_{difference}$ to PAT$_{shared}$ averaged across all patients as a function of the distance (expressed in mm) from the resection for functional (red circles) and anatomical images (blue circles). The values of the anatomical images are normalized to range of the values of the functional images. Error bars show the standard error of the mean. Power functions are fitted to the variability of the functional (red line) and anatomical images (blue line).
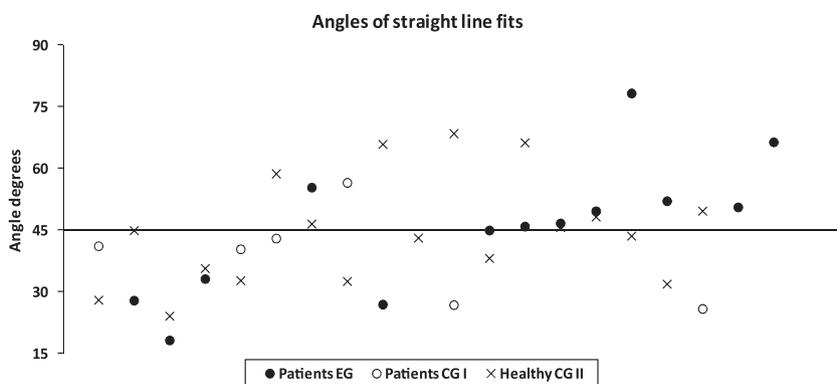
Fig. 6 – Angles of the straight line fits on the regressor coefficients (b-values) for patients' experimental (EG, *filled circles*) and control group (CG I, *open circles*), and healthy subjects (CG II, *crosses*). A slope of 45° indicates no global changes in the underlying BOLD amplitudes. Error bars are not shown as they were very small (largest error is .871°).

systematic between-session global changes in underlying BOLD amplitude (t-test against 45°) for the patients' experimental group [EG mean angle = 46.51°; $t_{(17)}$ = .36; p = .726] or control group [CG I mean angle = 39.07°; $t_{(5)}$ = 1.36; p = .232], nor for the healthy subjects [CG II mean angle = 44.81°; $t_{(17)}$ = .06; p = .951]. Univariate analysis showed no differences between the three groups in underlying BOLD amplitude global changes [$F_{(2,35)}$ = .59; p = .559]. Nevertheless, the variability in global underlying BOLD amplitudes was large; 56.18% for EG, 38.35% for CG I, and 41.31% for CG II, which also varied substantially between subjects (SD = 63.67% for EG, SD = 31.52% for CG I, and SD = 35.54% for CG II). In summary, our results suggest no systematic global changes in BOLD amplitude following surgery. However, global changes in the underlying BOLD amplitudes did frequently occur in individual patients and varied substantially between them.

3.3. Performance data

The fMRI task performance data that were acquired during the non-language blocks were analysed to check for compliance differences between the two scanning sessions and between the three groups. For each scanning session, the proportion of the times a subject pressed the button to the times requested to press a button was calculated. These values were compared by means of a repeated measures ANOVA analysis, which did not show a session effect [$F_{(1, 35)}$ = .02; p = .878], group effect [$F_{(2, 35)}$ = 2.49; p = .098], or interaction effect [$F_{(2, 35)}$ = .18; p = .833].

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4. Discussion

This study was performed to assess whether the recovery of surgery-induced language impairments in left sided low-grade glioma patients is associated with inter-hemispheric language reorganization. Analyses specifically addressed whether surgery specifically affected the spatial pattern of activation in functional homologue areas in the healthy, right brain hemisphere. In almost all of the left hemisphere patients language deficits were encountered during and immediately after surgery. Left sided glioma patients showed a

similar pattern of brain activation (PAT$_{shared}$) as right sided glioma patients and healthy control subjects before and after surgery, and a larger amount of changes in the activation pattern (PAT$_{difference}$) following surgery as compared to healthy subjects. The larger changes in the pattern of activation were however not specific for contratumoural areas and were also present in patients with a right sided glioma. Closer inspection revealed that changes in the activation pattern were highest in brain areas close to the surgical resection and decreased with the distance to the surgical resection. These changes in the activation pattern were however unrelated to functional variation following surgery as measured with neuropsychological testing. Because a decrease of variability with the distance to the surgical resection was also seen for the amount of anatomical mismatch, most of the changes for the spatial pattern of activation could be explained by the brain shift. *Whole brain* changes in the amplitude of activation did frequently occur in individual patients as well as control subjects, but no systematic effects were found following surgery.

The present study failed to provide evidence for surgery-induced functional reorganization specific to language homologue brain areas in the healthy hemisphere in glioma patients. This finding contrasts with results from several previous studies (Bonelli et al., 2012; Krainik et al., 2004; Roux et al., 2000; Sarubbo et al., 2012; Shinoura et al., 2006). Moreover, our findings indirectly suggest that immediate postoperative deficit observed in glioma patients may after all be associated with transient oedema or temporary damage to (sub)cortical neural circuits next to the resection area, contradicting recent reports (Duffau, 2012; Duffau et al., 2003). A potential source of the difference between our and previous results could be the analysis method. We specifically focused on changes in the pattern of activation which may be a more direct measure of functional reorganization than a direct pre- and post-surgery activity comparison with a statistical mapping software. Functional reorganization would change the functional architecture of the brain, and therefore the pattern of activation instead of the whole brain level of activation. Compared to the whole brain level of activation, changes in the pattern of activation are therefore conceptually a more plausible reflection of a change in brain function, and are less

likely confounded by effects of task compliance or fatigue. The LI technique, used as an alternative to ours, as well did not show signs of functional reorganization. Moreover, there is recent evidence that activity in language homologue brain areas is not always associated with functional reorganization (Baumgaertner, Hartwigsen, & Roman, 2012; Perrone-Bertolotti et al., 2012; Tyler, Wright, Randall, Marslen-Wilson, & Stamatakis, 2010).

We found an increase in changes in the activation pattern in patients in brain areas close to the tumour. These changes were unrelated to neuropsychological changes following surgery. Although perilesional functional reorganization after surgery could theoretically exist, it cannot be distinguished from coregistration error and brain shift. Coregistration error between sessions could be the result of the tumour resection even in absence of brain shift, due to local changes in the intensity of functional images (Power, Barnes, Snyder, Schlaggar, & Petersen, 2012). Our data suggest that in patients most of the perilesional increase in changes in the activation pattern is caused by the brain shift. This shift is a normal consequence of surgery, especially when the amount of extracted tissue is large. The brain shift causes anatomical misalignment between the scanning sessions (Hartkens et al., 2003; Hill et al., 1998; Khan et al., 2008; Miyagi et al., 2007). The anatomical misalignment in turn causes an apparent increase in variability of the spatial pattern of activation. While non-rigid registration methods have been proposed to properly match the tumoural hemisphere, in order to do so they deform the healthy hemisphere (Periaswamy & Farid, 2006; Zacharaki, Hogea, Shen, Biros, & Davatzikos, 2009). A perfect match at voxel level therefore may not be realistic even with the existing registration methods that report displacement errors as high as 3 voxels (Chitphakdithai & Duncan, 2010). New registration methods that will be able to (almost) perfectly match functional images of patients with large lesions may be thus beneficial to the analysis approach used in this study. It should be noted that we cannot fully determine whether reorganization has taken place surrounding the lesion, hence such an effect of surgery cannot be excluded. In the present study we specifically focussed on hemispheric changes.

Whole brain changes in the amplitude of the underlying activation pattern occurred frequently in individual patients following surgery as well as in healthy subjects. Though no systematic effects were found at the group level, the evidence for these whole brain changes suggests caution in the use of estimates of the BOLD signal amplitude (i.e., *b*-values) to compare or classify individual patients. Even large fluctuations in amplitudes of BOLD responses can be part of normal within subject variation (Raemaekers et al., 2012) instead of being a reflection of functional reorganization. Whole brain variations could thus theoretically have confounded previous case reports (Sarubbo et al., 2012; Shinoura et al., 2006).

5.   Conclusions

To conclude, we found no evidence for specific inter-hemispheric language functional reorganization in low-grade glioma patients following surgery. The functional variability that we found in brain areas close to the tumour could mostly be explained by the anatomical variability caused by the brain shift following surgery. Perilesional reorganization, however, cannot be excluded. Caution is suggested when interpreting results based on the amplitude of the underlying activation pattern as this is found to vary substantially in individual patients as well as healthy subjects. The study suggests that transient post-surgical language deficits are caused by transient disruption of neurophysiology or of (sub)cortical neural circuits. Language recovery therefore involves recovery of functioning of the presurgical language system.

Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.cortex.2014.11.002.

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