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RESEARCH ARTICLE

fMRI evaluation of hemispheric language dominance using various methods of laterality index calculation

Pavel Chlebus · Michal Mikl · Milan Brázdil · Marta Pažourková · Petr Krupa · Ivan Rektor

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Abstract Several functional MR imaging studies evaluating the lateralisation of linguistic functions in patients who underwent Wada testing have been reported. There is extensive variance in the Laterality index (LI) calculation across the studies, and the optimal calculation method remains unclear. We attempted to calculate the LI in different ways in the same subjects, in order to find the LI calculation method with the highest correlation to the Wada test. Fifteen patients (10 females, 5 males) suffering from medically intractable temporal lobe epilepsy (TLE) (12 left, 3 right) were admitted for the study. The patients underwent a standardized bilateral intracarotid short-acting barbiturate test. Language testing included spontaneous speech, oral comprehension, reading, object and picture naming, and repetition. All the tasks were scored separately in order to increase the possibility of correlation between Wada and LI. A silent phonemic verbal fluency task (VFT) was used as a language paradigm for functional measurement. Regions of interest (ROIs), with a known association with language function (Broca's area, the lateral prefrontal cortex, etc.), were defined. First, the LIs were calculated from the ROIs using a previously reported method (simple suprathreshold count). Next, we used several new methods of LI calculation (*t*–weighting of voxels, methods independent of the choice of the statistical threshold, etc.) The most significant correlation with Wada was proven in the LIs that were evaluated from Broca's area (up to $R = 0.94$, $P = 1 \times 10^{-7}$). However, the new LI calculation methods used in the present study did not produce a statistically significant benefit in comparison to previously reported methods.

Keywords Language · Laterality index · Temporal lobe epilepsy · fMRI · Wada test

P. Chlebus (✉) · M. Mikl · M. Brázdil · I. Rektor
Department of Neurology, Masaryk University,
St. Anne's University Hospital, Pekařská 53,
Brno 65691, Czech Republic
e-mail: chlepa@centrum.cz

P. Chlebus · M. Pažourková · P. Krupa
Diagnostic Imaging Clinic, Masaryk University,
St. Anne's University Hospital,
Brno 65691, Czech Republic

M. Mikl
Department of Biomedical Engineering,
FEEC, Brno University of Technology,
Brno Czech Republic

Introduction

Defining language lateralisation is important in order to minimize the risk of postoperative functional deficit in patients surgically treated in the language dominant hemisphere. In surgery candidates for intractable temporal lobe epilepsy (TLE), this is commonly done with the Wada test (Intracarotid amobarbital procedure), which is the "gold standard" for assessing hemispheric language dominance (Rausch and Walsh 1984; Rey et al. 1988; Risse et al. 1997; Springer et al. 1999). However, the Wada test has some drawbacks: possible angiographic procedure complications, pitfalls in interpretation of the results, etc. (Dion et al. 1987; Risse et al. 1997). These difficulties underlie the growing interest in fMRI as a non-invasive alternative for Wada testing. Several functional MR imaging studies evaluating the lateralisation of linguistic functions in TLE patients (who underwent Wada testing) have been reported (Springer et al. 1999; Carpentier et al. 2001; Rutten et al. 2002a; Adcock et al. 2003; Sabbah et al. 2003). There is usually a good correlation between the results from these two methodologies, but the correlation is not perfect. High concordance is found between fMRI and Wada test results in patients with left hemispheric language dominance (Adcock et al. 2003; Sabbah et al. 2003). However, fMRI fails to completely identify the persons who are identified through Wada testing to have atypical (i.e. right and mixed) language dominance (Rutten et al. 2002a; Adcock et al. 2003). This could be partly a methodological issue. First, the use of various types of language tasks (most often based either on word fluency or on semantic decision) produce different patterns of language-related fMRI activations. Second, there is a limited possibility of correlation between these two modalities. The Wada test involves a reversible pharmacologic deactivation of the language cortex critical for the task, but only in the frame of the large cortical area supplied by ACI, which leads to the categorisation of language laterality (left, right or mixed). Conversely, fMRI provides more detailed information about the localisation of language cortex, but also identifies areas that are not critical for the language processing. In addition, the results of linguistic function lateralisation in the Laterality index (LI) form are on a continuous scale. In the present study, we focused in detail on the methodology of fMRI LI calculation. We investigated different methods of quantifying brain activity from the fMRI data in order to assess the best correlation with the Wada test results. A silent form of a verbal fluency task (VFT) was chosen as a language paradigm. Despite its simplicity, this task was proven to be the most reliably lateralizing one (Benson et al. 1999). In terms of good reproducibility (Brannen et al. 2001; Adcock et al. 2003) and potential clinical applicability, it is currently regarded as the best option in fMRI studies on global language functions. Language production involves a distributed cortical network with specific functions processed in different regions of the brain (Mesulam 1990; Price 2000). Further, representation of different language functions in different hemispheres has been reported in Wada test patients (Loring et al. 1990; Risse et al. 1997). For this reason, and in order to increase the possibility of correlation, the linguistic functions (comprehension, reading, object and picture naming, repetition, and spontaneous speech) were scored separately, and Wada laterality index (WLI) was counted and used for correlation with fMRI data results.

Methods

Subjects

Fifteen patients (10 females, 5 males) suffering from medically intractable epilepsy were admitted to the study. The mean age was 31.13 (SD = 6.28). All of the patients had been routinely investigated within the epilepsy surgery program (high-resolution MRI, interictal SPECT, long-term semi-invasive video-EEG monitoring, neuropsychological examination); all of them preoperatively underwent a standardized bilateral intracarotid short-acting barbiturate procedure to assess the lateralisation of language and memory functions. The epileptogenic zone was located in the left temporal lobe in 12 patients (11 of them with findings of mesial temporal sclerosis (MTS) on MRI), and in the right temporal lobe in three patients (two of them with MTS). Only two patients had evidence of early brain disease (left hemisphere not directly affected). More detailed information including handedness assessed with Edinburgh Handedness Inventory (Oldfield 1971) is given in Table 1. All patients subsequently underwent surgery (anteromedial temporal resection ipsilateral to the location of the epileptogenic zone) with no postoperative speech or memory deficit. Czech was the primary language of all subjects. All subjects gave their informed consent in accordance with the approval of local ethics committee.

Wada procedure and Wada laterality index (WLI) calculation

The patients underwent a standardized bilateral intracarotid short-acting barbiturate test on the same day. EEG and video recording were obtained during Wada testing. The standard dose was 4.5 mg of methohexital sodium. Each hemisphere was diffused separately with a minimal 15 min delay between the injections. Language testing included spontaneous speech, oral comprehension, reading, object and picture naming, and repetition. All the tasks were scored separately (1 = able, 0 = unable) and WLI was obtained by the formula: $\mathrm{WLI} = (L - P)/6 \times 100$. A WLI value of +100 reflected a complete left hemispheric language dominance; a WLI value of −100 reflected a complete right dominance. We also categorised language laterality (left, right, mixed). The formula mentioned above is more appropriate than the alternative: $\mathrm{WLI} = (L - P)/(L + P) \times 100$. The results are more polarized and closer to the categorisations defined by Wada.

Table 1 Patient characteristics

Subject no.	Sex	Age (years)	Dominant hand	MRI finding	Wada (cat.)	Wada (WLI)
1	M	40	R	MTS left	L	100
2	F	24	R	DNET, right TL	L	83
3	M	35	R	MTS left	L	66
4	F	40	R	MTS left	R	−100
5	F	43	R	MTS left	L	100
6	M	25	R	MTS left	R	−66
7	M	35	M	Cavernoma, left TL	L	100
8	F	32	R	MTS left	L	100
9	F	34	L	MTS left	R	−100
10	F	20	R	MTS left [a]	L	100
11	F	22	R	MTS left	L	66
12	F	32	R	MTS left [b]	L	100
13	M	31	L	Normal	L	100
14	F	25	R	MTS right	L	100
15	F	29	R	MTS right	L	100

MTS mesial temporal sclerosis, *DNET* dysembryoplastic neuroepithelial tumor, *TL* temporal lobe

[a] Patients with evidence of early brain disease—posttraumatic subdural hematoma complicated with meningoencephalitis at the age of 7 months

[b] Patients with evidence of early brain disease—obstructive hydrocephalus at the age of 5 years

Activation task

A silent phonemic verbal fluency task (VFT) was used as a language paradigm. We used an ABAB block design, with active tasks (A) alternating with periods of rest (B). Active as well as control blocks lasted 32 s. Five blocks of each condition were performed. In the active block, subjects silently generated as many words as possible, beginning with a letter that had been presented to them through the headphones (I, J, N, O and P). During the rest periods, subjects simply relaxed. Instructions with demonstrations were given before scanning. After scanning, subjects were asked whether they had performed the task successfully. If the answer was negative, the functional part of the measurement was repeated.

Image acquisition parameters

Imaging was performed on a 1.5 T MR scanner (Siemens Symphony—Erlangen, Germany) equipped with a Numaris four System (MRease). The functional images were acquired using a gradient echo, echoplanar (EPI) sequence with the following parameters: TR (scan repeat time) = 4,520 ms, TE = 40 ms, FOV = 220 mm, flip angle 90°, matrix size 64 × 64, slice thickness 3.5 mm, 32 transversal slices per scan, 71 scans per each functional measurement. High-resolution anatomical T1-weighted images, which served as a matrix for the functional imaging, were acquired using a 3D sequence with the parameters: TR = 1,700 ms, TE = 3.96 ms, FOV = 246 mm, flip angle 15°, resolution 512 × 512, slice thickness 1.17 mm,160 sagittal slices.

fMRI data analysis

A statistical parametric mapping (SPM99) program was used to analyze the fMRI data (Friston 1999). All the images were co-registered, normalized to fit into the standard anatomical space (MNI), and spatially smoothed (using a Gaussian filter kernel with FWHM = 6 mm). The voxel size generated from the above acquisition parameters was oversampled to 3 × 3 × 3 mm. The first twelve scans were skipped in order to reach a steady state of magnetisation. Statistical parametric maps were computed to detect activation using a general linear model voxel-wise analysis. A boxcar reference waveform convolved with a kernel that approximates the haemodynamic response curve was used as a regressor of specific effects in the imaging data. Specific hypotheses (activation > rest) were tested with a *t*-value (SPM {*t*}) at each voxel. The activation maps were superimposed over the high-resolution anatomical images to display the areas of brain activation. A confidence level of $P < 0.001$ uncorrected was used for checking the distribution of activation or artefacts (overview of evaluation possibility).

fMRI-derived laterality indexes (MRLI) calculation

Regions of interest (ROIs), either those regularly used for MRLI calculation (Springer et al. 1999; Nagata et al. 2001; Rutten et al. 2002a, b; Adcock et al. 2003; Stippich et al. 2003) or those with a known association with language function and generally activated during VFT performance, were defined (the whole hemisphere—WH; the anterior two-thirds of the hemisphere—ATT; the lateral part of ATT—LATT; the lateral prefrontal cortex—LPC; a random effect group analysis mask for 20 healthy right-handed volunteers from our previous study (Chlebus et al. 2003). In brief, activation in Broca's region (Brodmann´s area (BA) 44, 45) and adjacent prefrontal cortex (BA 46, 8, 9)—VM; Broca's area—BROCA; the cerebellum—CER; the supplementary motor cortex and the anterior cingulate gyrus—SMA + CIN). ROIs were formed as rectangular areas (block-shaped masks) including the desired cortical areas, or as masks using anatomical criteria according to Brodmann (Talairach brain) (Fig. 1). MRLI was calculated according to the previously reported method (Springer et al. 1999; Rutten et al. 2002a; Adcock et al. 2003; Sabbah et al. 2003): MRLI = $(L - P)/(L + P) \times 100$ (+100 = strong left hemisphere dominance; −100 = strong right hemisphere dominance) using several approaches:

1. Classical MRLIs—we used a simple suprathreshold count. For each ROI, the numbers of suprathreshold voxels (with $t = 2.5$, 3, 3.5, 4, 4.5 and 3.28 ($P = 0.001$); all uncorrected) were counted in the left (L) and right (R) hemisphere, and filled in the formula.
2. POMLIs—again, we used a simple suprathreshold count, but the thresholds were now defined as a percentage of maximum *t*-value (jointly for both sides) in the ROIs. We applied 40, 50, 60, 70, 80, and 90% thresholds (POMLIs 40, 50,60,70,80, and 90).
3. *t*-weighted MRLIs—we used *t*–weighting of voxels to increase the influence of voxels activated at higher statistical significance. Each voxel in the ROIs was weighted with a corresponding *t*-value (TWLIs), a square of *t*-value (PWLIs) and $e^{t-\text{value}}$ (EWLIs) before calculation.
4. Thresholdless MRLIs—we used methods which are not dependent on the choice of the statistical threshold (*t* resp. *P*-value). The laterality indexes were defined (calculated) from statistical parameters of *t*-values acquired from the corresponding ROIs of left and right hemisphere (negative *t*-values were excluded). We used the magnitudes of mean (MeanLIs), median (MedianLIs), and maximum (MaximumLIs).

Structural anatomical images of each subject were segmented into grey and white matter (Friston 1999). All types of MRLIs mentioned above were calculated for the whole brain activation (including, e.g. artefacts from large draining veins, WB MRLIs), and separately for the grey matter activation (GM MRLIs). Altogether, we evaluated sixty MRLIs from each of the ROIs.

Comparison between WLIs and MRLIs

In order to increase the possibility of correlation, the linguistic functions (comprehension, reading, object and picture naming, repetition, and spontaneous speech) were scored separately (see above). The WLIs and the corresponding sets of MRLIs acquired by the above-mentioned approaches were correlated using the Spearman rank correlation coefficient. To compare the results of two groups of correlation coefficients (e.g. all correlation coefficients from BROCA versus all correlation

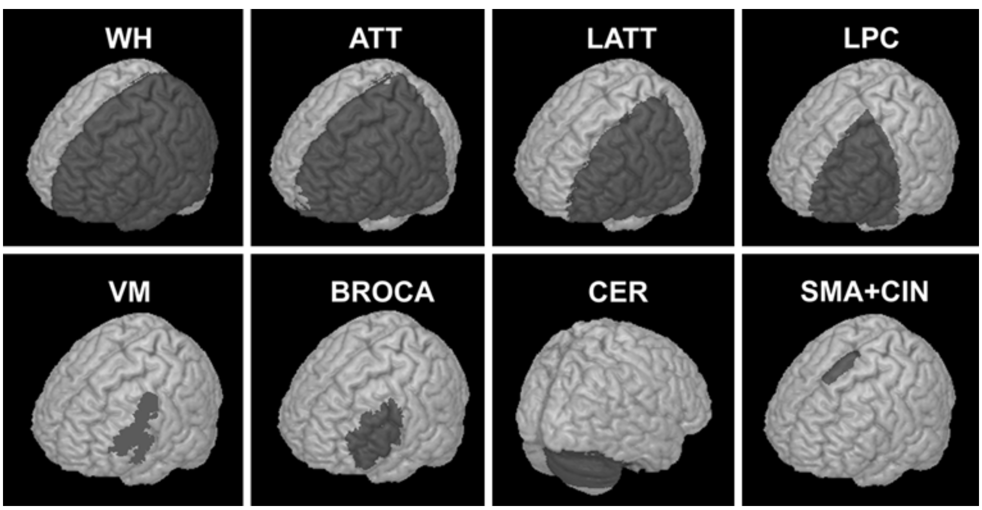

Fig. 1 Cortical areas belonging to individual ROIs (*WH* the whole hemisphere, *ATT* anterior two-thirds of the hemispheres; *LATT* lateral part of anterior two-thirds; *LPC* the lateral prefrontal cortex; *VM* activation mask of 20 right-handed volunteers calculated using one sample *t*-test; *BROCA* Broca's area; *CER* cerebellum; *SMA + CIN* the supplementary motor cortex and the anterior cingulum)

coefficients from ATT), we used a two-sample Student's *t*-test. A paired Student's *t*-test was used to compare all correlation coefficients from grey matter versus all correlation coefficients from the whole brain. For the comparison of individual correlation coefficients (e.g. WB, ATT, $t = 3.28$ versus POMLI 80), we used a standard test of difference between correlations. Statistics were obtained using the routines included in the Statistica program (StatSoft Inc., Tulsa, OK, USA).

Results

Wada test results

Based on the Wada categorisation, 12 patients (nine with left TLE, three with right TLE) were found to have left hemispheric dominance for language, whereas three (all with left TLE) patients had a right dominance. More detailed results, including the appropriate WLIs, can be seen in Table 2.

Patterns of fMRI activation during verbal fluency task

The patterns of activation in all subjects were in accordance with previously reported studies (Yetkin et al. 1995; Schlosser et al. 1998; Springer et al. 1999; Brázdil et al. 2005). The left inferior frontal gyrus (IFG), including BA 44 and 45 (i.e. Broca's area), was the most consistently activated region across the patients. The response was unilaterally left for nine subjects, unilaterally right for two subjects, and bilateral for two subjects (evaluated at $t = 3.28$; uncorrected). The frontal lobe activation usually spread ventrally (BA 10, 46) and superiorly (BA 6, 8, 9) into the adjacent prefrontal cortex. Other significant activation was found in the cerebellar cortex (14 subjects, usually contralateral to the activation of IFG). Less prominent clusters of activation were seen in the anterior cingulate gyri (BA 24, 32) (10 subjects, most with bilateral activation), the middle and inferior temporal gyri (five subjects, four left- and one right-sided activation), the hippocampus (six subjects, usually ipsilateral to the activation of IFG) and the left-sided lobulus parietalis superior (two subjects).

Comparison between WLI and MRLI

MRLIs calculated as described from the majority of the ROIs significantly correlated with Wada test results (WLI). The most significant correlation was proven in the MRLIs that were evaluated from Broca's area (up to $R = 0.94$; median $R = 0.84$). A slightly lower statistical significance of correlation showed MRLIs from

Table 2 A review of the best correlating MRILIs from individual ROIs with correlation parameters, and values of MRILIs for individual subjects. Categorisation of the results according to Springer et al. (1999) is represented by colour. *Yellow* left hemisphere language dominance, MRLI or WLI > 20; *Red* right hemisphere language dominance, MRLI or WLI < −20; *Blue* mixed language dominance, MRLI or WLI from −20 to 20

	Wada (cat.)	Wada (WLI)	WH	ATT	LATT	LPC	VM	Broca	CER	SMA+CIN
Type of MRLI	-	-	Classic. LI (WB)	Classic. LI (WB)	Classic. LI (WB)	Classic. LI (WB)	Median LI (GM)	POMLI 80 (WB)	Mean LI (WB)	POMLI 40 (WB)
Threshold	-	-	3.5	3.28	2.5	3.0	-	-	-	-
Correlation	-	-	$R=0.86$, $p=3.3\times10^{-5}$	$R=0.87$ $p=1.5\times10^{-5}$	$R=0.77$, $p=7.6\times10^{-4}$	$R=0.81$, $p=1.9\times10^{-5}$	$R=0.85$, $p=5.5\times10^{-5}$	$R=0.94$ $p=1\times10^{-7}$	$R=0.77$, $p=6.8\times10^{-4}$	$R=0.64$, $p=1.1\times10^{-2}$
Sub. No.1	L	100	55	51	62	75	38	100	21	16
2	L	83	27	17	45	48	12	100	-1	6
3	L	66	11	15	17	34	14	60	0	27
4	R	-100	-17	-39	-59	-51	-35	-100	-5	-33
5	L	100	42	34	39	43	33	100	21	12
6	R	-66	4	7	18	13	0	-100	3	0
7	L	100	42	50	50	54	34	100	22	38
8	L	100	72	34	37	71	20	100	5	31
9	R	-100	-39	-36	-24	-31	-14	-100	-5	-15
10	L	100	30	21	30	62	27	100	-2	11
11	L	66	4	1	13	28	11	60	-2	-10
12	L	100	63	55	46	52	29	100	26	24
13	L	100	29	29	34	72	36	100	8	7
14	L	100	23	21	23	28	12	100	4	-9
15	L	100	61	63	72	75	29	100	27	18

ATT (up to $R = 0.87$; median $R = 0.78$), WH (up to $R = 0.86$; median 0.77), LATT (up to $R = 0.77$; median 0.69), VM (up to $R = 0.75$; median $R = 0.64$), and LPC (up to $R = 0.82$, median 0.72). MRLIs evaluated from the cerebellum showed generally lower statistical correlation with WLI (up to $R = 0.78$; 0.57). SMA + CIN MRLIs showed only a weak correlation (up to $R = 0.64$; median 0.48), as we expected from the obtained patterns of activation in individual subjects. The summary of the results is given in Fig. 2 and Table 2. The impact of *t*-value thresholding on the correlation of MRLIs (Classical MRLIs, TWLIs, PWLIs, EWLIs) with WLI was investigated. The most appropriate statistical threshold for the majority of ROIs to obtain the data for MRLI calculation appeared to be between $t = 3.28$ ($P = 0.001$) and four ($P = 0.00012$). The only exception was the cerebellum, where $t = 2.5$ ($P = 0.008$) was proven as the most profitable threshold. The dependence of thresholding on correlation for Broca's area and the cerebellum is given in Fig. 3. The usage of percentage thresholds (POMLIs) generally did not produce a relevant benefit. The statistical significance of the correlation was at the same level as or lower than the rest of the MRLIs in the individual ROIs. Only the POMLIs from Broca's area behaved differently. POMLI 80 showed the highest correlation of all, but the difference compared with the standard method used for LI calculation (WB, ATT, $t = 3.28$) was not statistically significant ($P = 0.193$). The dependence of correlation on percentage thresholds is summarized in Fig. 4. Weighting of voxels with a corresponding *t*-value (TWLI), the square of *t*-value (PWLI) or $e^{t\text{-value}}$ (EWLI) also did not produce the expected benefit. The best results were produced by *t*-weighted MRLIs; these were without any drift in statistical significance against the standard method of MRLI calculation. Thresholdless methods of MRLI calculation were also without relevant contribution. A statistical comparison of all correlation coefficients from WB and GM did not prove a significant difference between these two groups of the data ($P = 0.39$). The results for individual ROIs did not show a statistically significant difference. Nevertheless, the correlation of WB MRLIs was generally slightly higher.

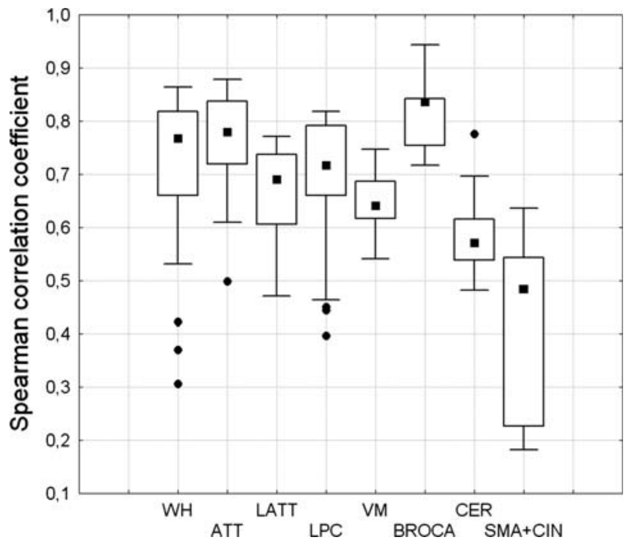

Fig. 2 The summary of the results. The set of correlation coefficients from individual ROIs and their statistical parameters (median, 25–75% percentile, outlying and non-outlying values)

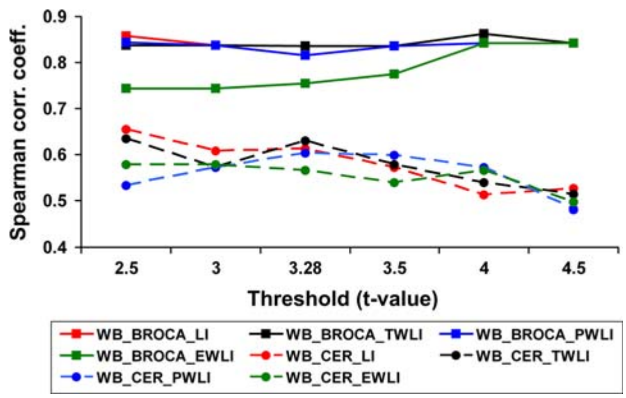

Fig. 3 The dependence of *t*–value thresholding for correlating the WLI and MRLIs from BROCA's area and the cerebellum

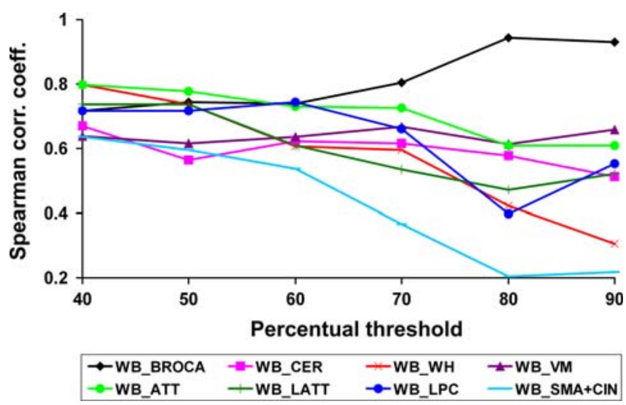

Fig. 4 The correlation between WLI and POMLIs for various ROIs. The dependence on percentage thresholds

Discussion

The idea of large-scale cognitive networks is a highly promising one in contemporary theories of cognition. The elementary functions (language articulation, phonetics, syntax, semantics, etc.) are localized in discrete cortical regions, and complex functions (e.g. speech comprehension) involve the parallel processing of information in widespread networks of the whole brain (Mesulam 1990; Price 2000; Dogil et al. 2002). The relative lateralisation of the language network that is observed with fMRI studies suggests that language lateralisation is a continuous, rather than a dichotomous, variable (Springer et al. 1999; Rutten et al. 2002a), while the classical Wada test provides categorisations for hemispheric language dominance (left, right, mixed). This leads to a limited possibility of correlation between the results of these two methodologies. Recent studies have solved this problem with empirical chosen cut-off values for the LI to classify fMRI activity in individual subjects as left, right, or mixed hemisphere dominant for language (Springer et al. 1999; Rutten et al. 2002a; Sabbah et al. 2003). Generally, the results of correlation are good, but not perfect. The LI calculated from fMRI measurement often fails to identify subjects with atypical (right or mixed) language dominance as revealed with the Wada test (Rutten et al. 2002a; Adcock et al. 2003). However, previously published papers have referred to a high incidence of atypical hemispheric language dominance just in TLE patients (Loring et al. 1990; Springer et al. 1999). The discrepancy between LI and Wada test results can be caused by deficiencies in both the Wada and fMRI methodologies. First, the Wada test is not actually a standardized procedure. There are differences in almost every part of the methodology, including the categorisation rules. A review of Wada literature shows an extremely wide incidence of atypical language dominance (right or mixed), from 4 to 37% in right-handed and from 25 to 52% in left-handed TLE patients (Risse et al. 1997). Despite its position as a “clinical gold standard”, it has not been definitively proven whether Wada testing is a more accurate predictor for “true” language lateralisation than fMRI (Rutten et al. 2002a). Some previous studies reported a dissociation of expressive and receptive language function (Kurthen et al. 1992) or naming and sequenced speech (Rasmussen and Nilner 1977) in the two hemispheres in TLE patients during a Wada procedure. In the study by (Risse et al. 1997), the variable distribution in the two hemispheres was proven in four language functions: sequenced speech, naming, comprehension, and reading (Risse et al. 1997). These results support the hypothesis that the language dominance as determined by Wada testing can be scaled into more degrees than merely left, right or mixed dominance. This allows a better possibility of correlation with continuous variable such as MRLI. The situation with fMRI procedures is even more complicated. Different language activation tasks or a combination of tasks are used in order to localize cortical regions critical for the language processing. Methods of assessing language lateralisation from fMRI activation also differ markedly (Springer et al. 1999; Nagata et al. 2001; Rutten et al. 2002a, b; Adcock et al. 2003; Stippich et al. 2003). However, an optimized clinical functional magnetic resonance imaging protocol which would safely determine hemispheric language dominance has not yet been found. We chose a silent form of VFT as an fMRI language paradigm. Despite its simplicity, this task was proven to be the most reliably lateralizing one, and probably represents the best choice in studies on global language functions (Benson et al. 1999). We are conscious that VFT presents only a limited opportunity to identify activation in the temporoparietal region, including Wernicke’s area. Activation paradigms, such as semantic decision task, language comprehension tasks, or combined task analysis lead to robust activation in Wernicke’s area (Binder et al. 1997; Carpentier et al. 2001; Rutten et al. 2002a). Nevertheless, temporoparietal activation seems not to be a good predictor for the determination of hemispheric language dominance in epileptic patients (Rutten et al. 2002a).

In our study, we investigated different methods of quantifying the brain activity revealed in the fMRI data, in order to assess the best method of correlation with Wada test results. In most of the fMRI studies concerning language lateralisation, MRLI calculation is not the central aim of the work. These studies usually employ a standard method of calculation from the suprathreshold ($P = 0.001$, uncorrected) voxels of the whole hemisphere using the formula: MRLI = $(L\text{-}R)/(L + R) \times 100$ (Springer et al. 1999; Sabbah et al. 2003). However, this method of calculation has several drawbacks. Not all the regions activated during the performance of language paradigms are related to language. Also VFT used in our study is not pure language task, but has substantial components of executive processing or verbal memory function (Price et al. 2000; Fackowiak et al. 2003). It has been demonstrated that the MRLIs from language regions were significantly higher than corresponding MRLIs acquired from the whole hemisphere (Rutten et al. 2002b). This implies (in healthy volunteers in whom we are searching a priori for maximal laterality) that critical language areas are more often located in defined language regions, which is in agreement with the results of lesional studies. Similar to previous studies (Nagata et al. 2001; Rutten et al. 2002a, Adcock et al. 2003), we have defined various ROIs that have a known association with language function and are generally activated during VFT for MRLI calculation (see above). As we expected, MRLIs from the majority of the ROIs or their combinations significantly correlated with Wada test results (WLI). The best correlation with Wada was proven in the MRLIs that were evaluated from Broca’s area. Although the results were better than in the case of standard MRLI calculation method (WB, ATT, $t = 3.28$), or in comparison with some other ROIs (ATT, WH, VM, LPC) used in our work, the difference was not statistically significant (Fig. 2) and our results, with a relatively small sample of subjects, should not be overestimated. If we accept that both of the methods that were compared in our study (fMRI and WLI) evaluate the lateralisation of the global language networks, we might be able to expect better results in correlation for larger cortical areas (WH, ATT, LATT, LPC) than for Broca's area separately. On the other hand, our patients are almost strong left or right language dominant (WLI values: −100, −66, 66, 83 or 100), thereby it is no surprise the best correlation of WLI with most polarized MRLIs from Broca´s area (Table 2). In summary, the ROIs that included Broca's area correlated better with hemispheric language dominance (as revealed by Wada test) than the other investigated ROIs (SMA + CIN, CER). Aside from the regions generally activated during VFT performance (Benson et al. 1999; Adcock et al. 2003; Sabbah et al. 2003), relatively frequent activation of the hippocampus seemed to be interesting. Although it was not the purpose of this paper, something about the possible modification of neural networks for language in TLE patients should be mentioned. It has been repeatedly proven the impact of epileptic seizures or subclinical epileptiform activity on intehemispheric reorganisation of language (Springer et al. 1999; Adcock et al. 2003; Brázdil et al. 2005). Recent studies even suppose critical role of mesiotemporal structures (Janszky et al. 2003; Liégeois et al. 2004) or even hippocampus (Weber et al. 2006) in formation of language-related neuronal network. However, we have found no coupling of hippocampus activation and the lateralisation of the language function in our study.

The standard method of MRLI calculation cannot evaluate weakly activated voxels, which can also play an important role in language functions. For this reason, we used various t-value thresholds ($2.5 < t < 4.5$) for calculation. For most of the ROIs, MRLIs increased when the statistical threshold became more stringent, which is in accordance with previous studies (Rutten et al. 2002b; Adcock et al. 2003) and produces an effect similar to that of the specific language ROIs mentioned above. However, the dependence of thresholding on correlation with WLI was not statistically significant (Fig. 3). All the suprathresholds voxels have the same power in MRLI calculation. Therefore, we wanted to favour the voxels that are activated with a higher statistical significance during VFT (statistical weighting). Although the correlation of this group of MRLIs (TWLIs, PWLIs and EWLIs) with WLI was good, there was no advance compared with standard methods of MRLI calculation. We aimed to experimentally eliminate the impact of arbitrary thresholding (POMLIs, MeanLI, MedianLI, and MaximumLI). Dependence on the arbitrary choice of threshold is a potential problem for measurements based on the extent of activation (Adcock et al. 2003). Threshold dependent MRLI calculation can also influence interindividual comparision of MRLI, if we realize considerable differences in values of t-statistics in individual subjects (Rutten et al. 2002b). Unfortunately, these results did not produce the expected benefit. We also tried to use some more sophisticated methods of thresholdless MRLI calculation from a recently published study (Nagata et al. 2001), but the results were not optimal. The hypothetical explanation of different results can be found in the different sample of subjects (healthy volunteers) in the study.

Despite a nearly identical degree of correlation with WLI, the potential of individual MRLIs for categorisation seems to be different. For example, POMLI 80 from Broca's area could be very useful for clinical aplication. It safely distinguished between left and right language dominance in accordance with the Wada categorisation in our TLE patients (Table 2). In contrast, majority of MRLIs classified some of the patinets as mixed language dominant (Springer et al. 1999). It concerned mainly the patients with no clear left or right language lateralisation according to the Wada (WLI: −66, 66 and 83), which was very interesting (Table 2). However, the small number of subjects with atypical language dominance in our study (three right and zero mixed language dominance) prevented a precise evaluation of the concordance of fMRI (MRLIs) with Wada category results.

In conclusion, the most significant correlation with Wada was proven in the MRLIs that were evaluated from Broca's area. This ROI was also the best for categorisation of the language lateralisation in the TLE patients, which is in accordance with preceding papers (Lehéricy et al. 2000; Spreer et al. 2002). Generally, the new MRLI calculation methods (application of different ROIs, statistical weighing of voxels, thresholdless counting) used in the present study seem to be statistically at the same level or inferior to the standard calculation, and the degree of correlation with WLI is more dependent on the ROI used than on the type of statistical evaluation of the data (t-statistics). The question remains if it is ever possible to correlate these two modalities in this way. Although we attempted to approach fMRI and Wada methodologies and compare the neural network for language as a whole, there still remains fundamental differences, which cannot be ignored. Usage of MRLI and its approximation to Wada test result in evaluation of language dominance is certainly only temporary issue. Better understanding of language processing in the view of fMRI will lead to replacement of MRLI or even Wada test with a different method of fMRI data evaluation. At present seems to be interesting complex assessment of language network using approach of effective connectivity (Fu et al. 2006). Further research on this issue is suggested.

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