Functional MRI Evaluation of Language Dominance Compared with the Wada Test: a Review and a Novel Sentence Task

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Summary

Numerous studies tested whether functional magnetic resonance imaging (fMRI) is capable of replacing the Wada test for determination of language dominance. We reviewed 24 studies with 486 patients. The overall mean concordance rate is only about 90%. Furthermore, atypical language dominance is not reliably detected. The objectives of the present study were to develop and validate a new linguistic based fMRI task that specifically activates all putative essential language areas and reliably detects language dominance. The main components of language were assessed with three different tasks (rhyme, synonym, and sentence). It was hypothesized, that the novel sentence task would fulfil the objectives of the present study best because it contained all the main components of language processing, that is phonology, semantic, and syntax. FMRI was performed in healthy right- (n=13) and left-handed controls (n=8), and 20 patients at 1.5 T prior to neurosurgery. In controls, activations were quantified by an individual volume of interest analysis. Four neuroimagers tested a visual rating score in the patients group. Interrater agreement and concordance between fMRI and Wada test were calculated. As expected, the sentence task showed high sensitivity and specificity to activate all putative essential language areas. In healthy right-handed controls, the frontal language area was activated by the sentence and synonym task in 100%, and in 73% by the rhyme task. The temporal language area was activated in 100% by the sentence-, in 64% by the synonym-, and 55% by the rhyme task. The sentence task also reliably detected atypical language dominance. Because of low sensitivity and specificity, the rhyme task was not used in patients. In patients, interrater agreement was 0.90 for activations in the inferior frontal and 0.97 in the superior temporal gyrus. Correlation between the Wada test and fMRI was 0.86 for the sentence and 0.89 for the synonym task. For the sentence task, the Wada-test and fMRI were concordant in all cases in determining the hemisphere with greater language representation. Thus, our novel sentence task provides robust activations in all putative essential language areas and can be used for a simple clinical visual analysis in determination of language dominance.

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Keywords: Language dominance, Wada test, functional magnetic resonance imaging, review, clinical rating

Bestimmung der Sprachdominanz durch die funktionelle MRT im Vergleich zum Wada-Test: ein Literaturüberblick und eine neue Satzaufgabe

Eine grosse Anzahl von Studien prüfte, ob die funktionelle Magnetresonanztomographie (fMRT) in der Lage ist, den Wada-Test bei der Bestimmung der Sprachdominanz abzulösen. Wir geben einen Literaturüberblick über 24 Studien mit 486 Patienten. Die durchschnittliche Konkordanzrate beträgt lediglich ca. 90%. Darüber hinaus wird eine atypische Sprachdominanz nicht zuverlässig entdeckt. Das Rationale der vorliegenden Studie bestand darin, eine neue linguistisch basierte fMRT-Aufgabe zu entwickeln und zu validieren. Diese sollte spezifisch alle potenziell essenziellen Sprachgebiete aktivieren und die Sprachdominanz zuverlässig bestimmen. Mit drei verschiedenen Sprachparadigmen (Reime, Synonyme, Sätze) wurden die Hauptkomponenten der Sprachverarbeitung erfasst. Wir gingen davon aus, dass die neue Satzaufgabe am besten die

Anforderungen der aktuellen Studie erfüllt, da sie die wichtigsten Komponenten der Sprachverarbeitung beinhaltete, das heisst Phonologie, Semantik und Syntax. Bei gesunden rechts- (n=13) und links-händigen (n=8) Kontrollprobanden sowie bei 20 prächirurgischen Patienten wurde ein fMRT (1.5T) durchgeführt. Bei Kontrollprobanden wurden die Aktivierungen durch eine individuelle „Volume of interest"-Analyse quantifiziert. Bei den Patienten testeten vier Neuroradiologen ein visuelles Ratingverfahren. Wie erwartet, zeigte die Satzaufgabe eine hohe Sensitivität und Spezifität in der Aktivierung potenziell essenzieller Sprachgebiete. Frontale Sprachareale wurden bei 100% der rechtshändigen Kontrollprobanden durch die Satz- und Synonymaufgabe, und bei 73% durch die Reimaufgabe aktiviert. Temporale Sprachareale wurden bei 100% der Kontrollprobanden durch die Satz-, bei 64% durch die Synonym- und bei 55% durch die Reimaufgabe aktiviert. Die Satzaufgabe entdeckte auch zuverlässig eine atypische Sprachdominanz. Aufgrund einer zu geringen Sensitivität und Spezifität wurde die Reimaufgabe bei den Patienten nicht mehr durchgeführt. Bei den Patienten lag bei inferior frontalen Aktivierungen die Interrater-Übereinstimmung bei 0,90, bei Aktivierungen im Gyrus temporalis superior bei 0,97. Die Korrelation zwischen Wada-Test und fMRT betrug 0,86 für die Satz- und 0,89 für die Synonymaufgabe. Bei der Satzaufgabe stimmte die Bestimmung der Sprachdominanz mit dem Wada-Test und fMRT bei allen Patienten überein. Insgesamt zeigt also unsere neue Satzaufgabe stabile Aktivierungen in allen potenziell essenziellen Sprachgebieten und ist geeignet für eine einfache klinische visuelle Analyse zur Bestimmung der Sprachdominanz.

Schlüsselwörter: Sprachdominanz, Wada-Test, funktionelle Magnetresonanztomographie, Literaturüberblick, klinisches Rating

Détermination de la dominance pour le langage par IRM fonctionnelle en comparaison avec le test de Wada : une revue de la littérature et une nouvelle tâche syntaxique

De nombreuses études ont été menées afin de vérifier si l'imagerie fonctionnelle par résonance magnétique (IRMf) pouvait remplacer le test de Wada pour déterminer la dominance pour le langage. Nous faisons revue de la littérature portant sur 24 études et 486 sujets. Le taux de concordance moyen n'est que d'env. 90%. En plus, une dominance pour le langage atypique ne peut être repérée avec fiabilité. La motivation de la présente étude avait été de développer et de valider une nouvelle tâche syntactique pour l'imagerie IRMf. Son but spécifique consistait à activer toutes les aires de la parole potentiellement essentielles et de déterminer la dominance pour le langage de manière fiable. À l'aide de trois paradigmes linguistiques (rimes, synonymes, phrases), les composantes essentielles du traitement sémantique ont été testées. Notre hypothèse de travail était que la nouvelle tâche syntaxique « phrase » répondait le mieux aux besoins de l'étude actuelle, étant donné qu'elle contenait les composantes essentielles du traitement de la parole, à savoir : la phonologie, la sémantique et la syntaxe. Chez des sujets témoins sains droitiers (n=13) et gauchers (n=8), ainsi que chez 20 patients en attente d'une intervention chirurgicale, une fMRI (1.5/) a été effectuée. Chez les sujets témoins, les activations étaient quantifiées par une analyse individuelle du « volume d'intérêt ». Chez les patients, quatre neuroradiologues ont testé un procédé de classement visuel. Comme anticipé, la tâche syntaxique « phrase » affichait une grande sensitivité et spécificité dans l'activation des aires de la parole potentiellement essentielles. Les aires frontales de la parole étaient activées chez 100% des sujets témoins droitiers par la tâche de construction de phrases et de recherche de synonymes, et chez 73% pour la tâche de création de rimes. Les aires temporales de la parole étaient activées chez 100% des sujets témoins pour la tâche de création de phrases, chez 64% pour les synonymes et chez 55% pour les rimes. La tâche syntaxique « phrases » repérait aussi de manière fiable une dominance pour le langage atypique. En raison de la trop faible sensitivité et spécificité, la tâche « rime » n'a plus été proposée aux patients. Chez les patients, la concordance d'interclassement était de 0,90 en cas d'activations des aires frontales inférieures et de 0,97 en cas d'activations du gyrus temporal supérieur. La concordance entre le test de Wada et l'IRMf était de 0,86 pour la tâche « phrase » et de 0,89 pour la tâche « synonyme ». Pour la tâche « phrase », la détermination de la dominance pour le langage par le test de Wada et par TEPf concordait pour tous les patients. Globalement, notre nouvelle tâche « phrase » montre donc des activations stables dans toutes les aires de la parole potentiellement essentielles et elle convient à une analyse visuelle clinique simple visant à déterminer la dominance pour le langage.

Mots clés : Dominance linguistique, test de Wada, tomographie par résonance magnétique fonctionnelle, revue de la littérature, classement clinique

Introduction

We recently reported a Wada test validated fMRI study on language dominance using a novel sentence task [1]. Here we describe this study and the results more comprehensively. We additionally provide a comprehensive review of studies, which compared the concordance of the Wada test and fMRI in determination of language dominance.

Determination of language dominance is crucial prior to epilepsy surgery and any other neurosurgery close to language cortex in order to avoid postoperative deficits. Historically, the Wada test has been the standard for determination of language dominance [2]. Although still considered as a „gold standard" the Wada test has several important limitations because of its invasiveness [3, 4], difficulties related to its application and interpretation (e.g. in the case of arterial cross flow, excessive or too low sedation, emotional reactions of the patients) [5-8] or absence of spatial resolution. Methodological drawbacks of the Wada test include the limited time window to explore language functions during the procedure, the lack of normal control data and rather weak test-retest reliability [5, 9, 10]. Compared to alternative non-invasive approaches such as fMRI the Wada test is time consuming, requires more staff and is less cost effective (up to three times) [11, 12].

Considering all these drawbacks, the role of the Wada test as the clinical standard for determination of language dominance seems to be rather weak and has been increasingly challenged in recent years [13-15]. Therefore, the need to replace this procedure with less invasive and more reliable techniques has long been recognized. Due to its high availability, one of the most promising methods is fMRI.

The major difference between the Wada-Test and fMRI lies in the fact that the Wada-Test is an inactivation method blocking the function of one hemisphere, thus allowing to test the function of the non-anesthetized hemisphere. It therefore designates the hemisphere that is essential or nonessential for language. By contrast, fMRI is an activation method by providing information about which hemisphere (or set of brain regions) is activated more for a certain language task relative to a control task or rest. It may be that some of these hemispheric activations (or activated brain regions) are superfluous, that is not essential for language processing [16]. For instance, if fMRI shows bilateral activation this does not necessarily mean a bilateral distribution of language-essential cortex. It is possible, that it results from the co-activation of language or other cognitive-associated but not language-essential cortex contralateral to the dominant hemisphere [6, 12, 17].

Mistaking language-associated cortex or artificially highlighted regions for language-essential cortex may have relevant impact on the surgical strategies and thus on postoperative outcome [12, 17-19].

Therefore, the optimal fMRI design should not only be highly sensitive but also specific in activating the language dominant hemisphere, i.e. should reliably activate all putative essential language areas. Additionally, it should be able to detect atypical cerebral language organization, that is right and bilateral language dominance, which is a well-described phenomenon in epilepsy patients [20-22].

Brain regions are considered language-essential, if their lesion or dysfunction causes a characteristic aphasic syndrome. These language areas do not only comprise the ‚classical' Broca's (opercular part of the inferior frontal gyrus) and Wernicke's area (posterior superior temporal gyrus). In vascular aphasia, they also involve most of the inferior frontal (opercular and triangular part) and middle frontal gyrus, the anterior insula and subcortical regions in the case of Broca's aphasia [23-26]. In Wernicke's aphasia, the characteristic lesion involves the posterior superior and middle temporal gyrus as well as the inferior parietal lobe (posterior supramarginal and angular gyrus) including subjacent white matter [25-28]. The investigation of language localization with electrical stimulation mapping during neurosurgical operations [29-32] and in patients with primary progressive aphasia [33-35] additionally disclosed the anterior and inferior temporal cortex as essential language regions. In the following, we refer to the mentioned regions as language essential areas, and all other regions as language non-essential areas.

To evaluate studies comparing the Wada test with fMRI of language, we have listed them in a table in the appendix with a description of subject sample size, number of patients with left-, right- or bilateral language dominance, fMRI activation/control tasks employed, behavioural monitoring, region of interest, activation patterns, quantification scores, concordance, correlation and discordance between Wada-test and fMRI.

We found 24 studies with valid Wada tests and fMRI in 486 patients. In the Wada test 78% of the patients showed left and 22% atypical (right or bilateral) language dominance. This prevalence is similar to the pioneering work of Rasmussen and Milner [36], Loring and co-workers [21], and others [19, 37].

To determine hemispheric language dominance of the fMRI tasks, usually a language laterality index (LLI) is calculated as the difference between left and right activation divided by the sum of the two activations multiplied by 100, thus yielding scores from +100 (strong left hemisphere dominance) to -100 (strong right hemisphere dominance). In some studies somehow arbitrarily, fMRI-LLI cut-off scores between ±10 and ±26.5 (mean ±20) are used [38-47] to discriminate typical from atypical language dominant patients (for alternative methods see [17]). To facilitate clinical interpretations, a few studies have used an easier to perform clinical rating procedure based on visual interpretation of fMRI activation patterns. Four studies [44, 48-50] have investigated interrater agreements ranging from 0.36 – 1.0 with a fairly well mean of 0.85.

Taking the best concordance score between the Wada test and fMRI in each study, the overall mean concordance rate is 88.9% with a range of 55-100% (see summary at the end of the **Table in the appendix**). In five studies also correlation scores were calculated [7, 46, 51-53] with a mean correlation score of 0.93 (range 0.89 – 0.96) between Wada- and fMRI language laterality indices. If a single study with an extremely low concordance rate of only 55% is excluded [54] there seems to be no difference in concordance rates in studies using LLI (mean: 91%; range 79-100%) compared to studies using clinical ratings (mean: 88%; range 78-100%).

Note that the percentage of the overall discordance rates do not fully add to 100% to the percentage of the concordance rates, because in some studies discordance data are not given. The overall discordance score between Wada test and fMRI is higher in patients with atypical language dominance (5.7%) compared to patients with left-typical language dominance (2.5%; see the end of the **Table in the appendix**).

Most frequently, the fMRI probes consisted of different alternatives of a verbal fluency task. In these tasks, patients had to produce words from predefined letters or semantic categories, or have to produce verbs or rhymes from predefined nouns [38-41, 48, 51-57]. Neuropsychologically, verbal fluency tasks are considered relatively pure measures of lexical-semantic retrieval [58]. None of these studies incorporated an adequate control task. In no study, direct behavioural monitoring of task performance during fMRI acquisition was performed. Verbal fluency tasks seem only to be sensitive to activate putative anterior language areas. In all studies, more or less strong activations were found in the inferior frontal gyrus spreading to putative non-essential language regions of the dorsolateral prefrontal cortex and variably activating other regions like the supplementary motor area, posterior language areas, or subcortical regions. Concordance rates are in the usual range (mean 94%; range 83-100%) with discordance scores over-represented in patients with atypical (primarily bilateral) language dominance (mean 5%; range 0-17%) compared to left language dominance (mean 1%, range 0-6%). Overall, sensitivity of verbal fluency tasks to activate all putative essential language areas is low. Thus, these tasks seem not to be capable to reliably determine language laterality or activate all putative essential language areas.

Others administered different versions of a semantic decision task as fMRI probe. In some, patients had to decide if a given noun represents either a living or a nonliving object [42], is either of concrete or abstract nature [12], is a synonym to one of four other nouns [43] or if a given noun-pair is synonymous [59]. Using a decision task in which not only verbal-semantic decisions but also world-knowledge was assessed, Binder et al., 1996 [7] and Benke et al., 2006 [49] presented their participants nouns designating animal names or common objects. Patients had to decide if the animals are native to the United States and commonly used by humans, or if the objects are available in a supermarket and costs less than seven Euros, respectively. Gaillard et al., 2002 [44] used a semantic-lexical retrieval task in which object descriptions had to be named. With one exception [42], all of these studies incorporated a control task and direct behavioural monitoring of task performance during fMRI acquisition. Although, these tasks activate both putative anterior and posterior essential language areas, the sensitivity rate to activate both putative language areas on an individual basis is unknown. Additionally, they also activate putative non-essential language areas like the fronto-orbital cortex, the superior frontal gyrus, the cingulum, the temporal fusiform gyrus, the inferior temporal gyrus, the superior parietal lobule or the precuneus. These activations seem to be more frequent in studies in which broader semantic decisions are required [7, 49] compared to narrower semantic-verbal decisions [12, 42-44, 59]. Concordance rates are in the usual range (mean 87%; range 60-100%) with discordant scores similar in patients with left (4%; range 0-10%; not considering the study of Baciu et al., [42]) and atypical (4%; range 0-12%) language dominance.

One study used a phonological decision task [60] in which patients had to decide whether word-pairs rhymed. It activated primarily putative essential anterior, variably also putative posterior essential language regions, as well as putative non-essential language areas in the occipital and superior parietal lobe.

Several authors have tried to reduce the discordance rate between Wada test and fMRI by using a panel of tasks [45-47, 50, 61]. Although this holds true for certain single studies [e.g. 47, 50], the mean concordance rate (85%; range 79 – 90%) of these studies is in the usual range misclassifying patients with atypical language dominance (mean 10%; range 0-18%) more often than with typical language dominance (mean 5%; range 0-12%). Since most of these studies used the described fMRI tasks like verbal fluency tasks, semantic decision tasks, or naming, sensitivity to activate both putative language areas is similar as in the studies using only one task. It is noteworthy, that in two studies by Arora et al. [45] and Carpentier et al. [61] a semantic and syntactic decision task was used in which patients had to decide whether auditory presented sentences were semantically or syntactically correct. The authors report, that this study activated Broca's and Wernicke's area. Unfortunately, separate data for the semantic and the syntactic task are not given.

Taken together, numerous studies tested whether fMRI is capable of replacing the Wada test for determination of hemispheric language dominance. However, the overall concordance rate of the reviewed studies is only about 90%. Additionally, atypical hemispheric language dominance, which is relatively high in epilepsy patients, is not reliably detected.

Methodological concerns have been expressed regarding sample size, underlying lesion, functional reorganization, determination of language lateralization, input mode, task difficulty, fMRI threshold, and in particular behavioural monitoring and task design [6, 46, 49, 61-69]. A major problem in more than half of the studies is the fMRI design used.

As stressed by Swanson et al., 2007 [62], methodologically the usefulness of fMRI language maps depends on how well the probe and control tasks are designed to identify putative essential language areas with high specificity. Most of the fMRI language tasks are not based on linguistic considerations. Investigators tend to retain task paradigms known to them (e.g. verbal fluency tasks). A common methodological limitation is the failure to incorporate an adequate control task in the activation protocol to minimize unwanted mental activity. Since all reviewed studies used a subtraction technique, the control task should incorporate all mental or other processes involved in the activation task, without that of the interesting language component.

Thus, there is still no recommendation for a validated fMRI protocol that can be reliably used in surgery. The objectives of the present study were to develop and validate a new linguistic based fMRI-task that reliably lateralizes language and is sensitive to activate all putative essential language areas.

Recent advances in the study of language show that the language system seems to be conceived as a set of integrated but distinct subcomponents: phonology (the combination of individual speech sounds), semantics (the meaning of words), and syntax (the grammatical structure of sentences) [70, 71]. All studies comparing the validity of fMRI of language with the Wada tests used lexical-semantic retrieval processing in the form of fluency tasks and object naming, phonological, or semantic decision tasks as fMRI probe (see the **Table in the appendix**). Thus, syntactical processing as one main component of language was not evaluated yet.

To assess all the main components of language processing we designed a baseline (letter control task) and a novel sentence decision task. For reasons of comparison with other studies, we also incorporated a phonological and semantic decision task. It was hypothesized that the sentence task, which contained all the main components of language, should be able to reliably detect typical and atypical language organization and activates all putative (i.e. based on a priori

Table 1: Clinical data.

Patient	Age(y)/sex	Pathology (MRI)	Seizure focus/site	HLI[a]	LLI[b]
1	43/F	Mesiotemporal sclerosis	Right temporal	+100	+76
2	30/M	Subependymal heterotopia	Bilateral temporal	+100	0
3	34/M	Mesiotemporal sclerosis	Left temporal	+100	+100
4	39/F	Mesiotemporal sclerosis	Left temporal	+100	+100
5	33/M	Arteriovenous malformation	Left temporal	+100	+75
6	32/M	Cortical dysplasia	Left temporal	+29	+100
7	38/F	Astrocytoma	Right frontal	-53	+67
8	41/M	Glioma	Right frontal	-70	-36
9	38/F	Arteriovenous malformation	Left temporal	+100	+100
10	17/M	Mesiotemporal sclerosis	Left temporal	+100	+67
11	30/F	Mesiotemporal sclerosis	Right temporal	+100	+100
12	35/F	Dysembryoplastic neuroepithelioma	Right temporal	0	+100
13	37/F	Mesiotemporal sclerosis	Left temporal	-100	+80
14	30/F	Left frontal, left temporal and hippocampal lesions	Left frontal, left temporal, left hippocampal	+86	-80
15	29/M	Astrocytoma	Left temporal	+86	+68
16	22/M	Mesiotemporal sclerosis	Left temporal	+100	+87
17	39/F	Cavernoma	Left temporal	+100	+80
18	38/F	Cortical dysplasia	Left temporal	+30	+94
19	36/M	Arteriovenous malformation	Right temporal	+100	+100
20	52/M	Cavernoma	Right temporal	+45	+100

[a] Handedness laterality index; [b] Language laterality index based on the Wada testing (see text)

anatomical knowledge) essential language areas in the individual. Furthermore, we assumed that presurgical determination of language lateralization could be performed alternatively by a clinical rating procedure based on neuroanatomical representation of putative essential language areas.

Methods

Participants

To evaluate and validate the activation patterns in putative essential language areas, thirteen right-handed (6 females, 7 males; mean age 30.8 years) and eight left-handed (4 females, 4 males; mean age 33.0 years) healthy participants without neurological impairment and normal structural MRI were studied. Afterwards, twenty consecutive patients (10 females, 10 males; mean age 34.7 years), who were assessed for surgical treatment of medically intractable seizures (12 patients) or brain tumours giving rise to symptomatic seizures (8 patients) were studied with both fMRI and Wada testing (see **Table 1**). Handedness was assessed using a modification of the Edinburgh Handedness Inventory [72]. All participants were native German speakers and provided written informed consent according to a protocol approved by the local ethics committee.

Wada Test

We have performed the WADA test procedure according to Loring et al. [21]. The standard dose was 125 mg sodium amytal injected by hand over a 4- to 5-second interval. Language testing consisted of object naming, reading – and repetition of nouns. The number of total errors was calculated for each side of injection. Only trials conducted before return of motor functioning and EEG normalization were included in the calculation. A language lateralization index (LLI) was calculated as (L-R) / (L+R) x 100, with L and R are the percentage of correct responses (of the total possible) after injection of sodium amytal in the left and right hemisphere. This approach yields Wada-LLIs ranging between +100 (complete left language dominance) and -100 (complete right dominance), and indices in between reflecting varying degrees of language laterality. The Wada-LLIs are given in **Table 1** ranging in our patients from +100 to -80.

fMRI tasks

Material

To assess the main components of language we employed a baseline and three different language decision tasks on visually displayed stimuli: letter, rhyme, synonym, and sentence. All four tasks had an identical design: They consisted of pairs of items. Half of the trials required a same-response and half required a different-response. An overview of the fMRI language tasks is given in **Table 2**.

In the letter-decision task (baseline condition) engaging visual processing, participants determined whether pairs of consonant strings were identical. In the rhyme-decision task engaging visual and phonological processing, participants determined whether pairs of non-word strings rhymed. In the synonym-decision task engaging visual, phonological, and semantic information processing, participants determined whether pairs of words were synonymous. In the sentence-decision task, engaging visual, phonological, semantic, and syntactic information processing participants determined whether pairs of grammatically different sentences contained the same meaning.

The pairs of items were projected in a black boldface font on a white background, one item above the other. To keep general luminance constant across tasks, x-flankers were added to the left and right of each item. Since the sentence tasks made more eye-movement necessary, the horizontal position of each item of the pairs was presented randomly in an attempt to approximately hold this effect constant across the tasks. Note, that the rhyme task was not used in patients, since in healthy right-handed controls this task was not sensitive enough to activate putative essential tasks. The constructions of the tasks were as follows:

For the letter task pairs of consonant-strings, each string consisting of 6 different consonants randomly chosen from the alphabet were constructed, which were either identical (e.g. ‚Tqblms' and ‚Tqblms') or different with respect to only one consonant (10 pairs differing in the first consonants [e.g. ‚Pktgrs' and, Dktgrs'], 10 pairs differing in the second consonants [e.g. ‚Lfvjmp' and ‚Lbvjmp'], and so forth).

For the rhyme task pairs of pronounceable non-word strings, each string from 4 to 15 characters in length were constructed, which were (according to German orthographic pronunciation rules) either phonologically similar (e.g. ‚Xahre' and ‚Phare') or phonologically different (e.g. ‚Xahre' and ‚Tille'). Care was taken that orthography of the pairs were dissimilar. According to ratings by 10 normal subjects, the non-words had a low degree of association value to real words.

For the synonym task pairs of nouns, each from 4 to 15 characters in length were constructed, which were either semantically similar (synonyms, e.g. ‚idea' and

Table 2: fMRI design.

Task	Example	Correct Response	Putative processes engaged
Letter	xxxxxxx Cspwnh xxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxxxxxxxx Cspwnk xxxxxxxxx	≠	• visual
Rhyme	xxxxxxxxxxxxxxxxxxxxxxx Xahre xxxxxxxxxxxx xx Pfaare xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx	=	• visual • phonological
Synonym	xxxxxxxxxxxxxxx Decision xxxxxxxxxxxxxxxxxxx xxxxxx Condition xxxxxxxxxxxxxxxxxxxxxxxxxxx	≠	• visual • phonological • semantic
Sentence	x The woman with the bag loves the man xxxxxxxxx xx The woman with the bag is loved by the man xxxx	≠	• visual • phonological • semantic • syntactic

‚thought') or semantically different (non-synonyms; e.g. ‚decision' and ‚condition'). All nouns had a high degree of abstractness [73, 74].

For the sentence task pairs of syntactically varied sentences with the same content words were constructed, which denoted either the same (e.g. ‚The man with the bag kisses the woman' and ‚The man, who kisses the woman, has a bag') or a different (e.g. ‚The man with the bag kisses the woman' and ‚The man with the bag is kissed by the woman') meaning. All sentences had as their underlying form the simple subject - action (verb) - object structure. There were 10 different sentences denoting an interaction between two persons or objects (e.g. ‚The truck from Denmark passes the Mercedes'). All sentences were reversible, i.e. the object could also be the subject with the same plausibility. Syntactic variations referred to active / passive voice and center-embedded relative clause. Sentence pairs were constructed so that the meaning of at least one of the two sentences could not be denoted simply by semantically based heuristics (e.g. word order), but by an algorithmic analysis of the syntactic structure of the sentence (e.g. pair of items with active and passive voice).

Procedure

Participants were instructed to respond by pressing one of two pneumatic squeeze balls. Half of the participants indicated same-responses with the right hand, and different responses with the left hand. For the other half of subjects, this order was reversed. The subjects determined speed of presentation. After a response, the next trial was immediately presented. Error scores were recorded for each task. The trials in each task were arranged in a pseudorandom order with the constraint that no more than four same- or different-responses appeared consecutively.

Thus, in all tasks visual parameters (letter size, luminance, eye movements), decisions (same, different) and motor responses (left, right hand) were comparable, the sole difference between the tasks being the type of linguistic information engaged by each.

fMRI acquisition

All examinations were performed with a 1.5-T MRI (Siemens Magnetom Vision, Siemens Medical Systems, Erlangen, Germany) with a standard 4-channel head coil.

Functional data were acquired with a multi-slice single-shot T_2*-weighted echo planar imaging sequence (TR 6000 ms; TE 82 ms) including 30 slices and a voxel size of 1.56 x 1.56 x 4 mm; FOV = 192mm×192mm, matrix size = 128×128.

The fMRI-BOLD was performed including 68 runs with cycles of 24 s (language decision) and 24 s OFF (letter decision), repeated 8 times resulting in a total presentation time of 384 sec. All tasks alternations were trained beforehand in a practice session.

fMRI analysis

Analysis of the fMRI data was performed using a standard procedure provided by the BrainVoyager QX

1.2 (Brain Innovation, Maastricht, Netherlands, www.BrainVoyager.com). The first four images of the time-series were excluded from analysis to exclude a T1 saturation effect. Preprocessing of the images included the removal of low-frequency drifts, 3-D motion detection and correction and spatial smoothing with 6 mm FWHM. Voxelwise correlations between the BOLD signal and the predictor were computed using a General Linear Model (GLM). The six motion parameters derived from the fMRI preprocessing (translation and rotation in the X, Y and Z direction respectively) were used as covariates in the GLM. Correlation estimation was done with a threshold $p < 0.05$ corrected for multiple comparisons (family-wise errors) with $t > 3.1$ and minimum cluster threshold of 40 mm. For illustration, the images were additionally coregistered to an anatomical dataset.

Volume of interest analysis

In the developmental phase with healthy controls, we used a more fine-grained method of individual volume of interest (VOI) analysis to test the power of our language tasks to activate all putative language areas of the dominant hemisphere. A *priori* VOIs (see also the centre of **Figure 1**) were defined using the individual anatomical parcellation method described by Rademacher and co-workers [75]. The frontal lobe VOIs comprised the frontal pole (FP), the superior and middle frontal gyri (F1, F2), the opercular and triangular part of inferior frontal gyrus (F3o, F3t), the precentral (PRG), and the supplementary motor cortex (SMC). The temporal VOIs included the anterior and posterior superior (T1a, T1p) and middle (T2a, T2p) temporal gyrus as well as the most posterior temporo-occipital (TO) part of the middle temporal gyrus. Parietal VOIs included the postcentral gyrus (POG), the superior parietal lobule (SPL), the anterior and posterior supramarginal gyrus (SGa, SGp), the angular gyrus (AG), and the precuneus (PCN). In the occipital lobe, the occipital lateral gyri (OL) and the cuneus (CN) formed additional VOIs. Finally, the medial paralimbic VOIs comprised the paracingulate cortex (PAC) and cingulate gyrus (CG). We analyzed the percentage signal change relative to the control task average subjected to the typical statistical procedure in every VOI from all subjects, i.e. testing the null hypothesis of no change by calculation of z scores.

Although, from a scientific point of view the individual VOI approach has several advantages [76-78] it is very time-consuming. In today‘s clinical routine, neuroimagers perform fMRI studies almost daily, and with an increasing number of patients undergoing fMRI, it is important to provide simple and reproducible interpretations that are less time consuming and that can be easily carried out during clinical routine. Therefore, we further analyzed, if a simple clinical rating procedure produces reliable results, when interpreted by different raters. Thus, we tested the interrater reliability of four different neuroimagers blinded to the kind of fMRI language tasks in the interpretation of the fMRI images. Additionally we were interested how good this clinical rating corresponded to the LLI of the Wada test. Four independent neuroimagers were asked to determine the extent (independent of intensity) of BOLD correlates (statistical maps) in predetermined regions of interest (ROIs). The ROIs comprised the superior and middle frontal gyrus, the inferior frontal gyrus including the opercular and triangular part (Broca‘s area), the posterior superior and middle temporal gyrus (Wernicke‘s area), the inferior parietal lobule, and the precuneus/cuneus. If the ROI showed no signal increase, the rating was defined as 1. If approximately one or two thirds of the BOLD signal increase was found at the ROI, rating was 2 or 3, respectively. If the whole ROI was activated, rating was 4. Ratings were performed separately for each hemisphere and each task comparison. Based on these ratings, LLI for every ROI and every rater were calculated with the formula $(L-R)/3 \times 100$, where L and R are the rating scores for the left and right hemisphere. This approach yields LLIs ranging between +100 (complete left language dominance) and -100 (complete right dominance), and indices in between reflecting varying degrees of language laterality.

The graded rating of BOLD correlates in predefined ROIs allowed us to calculate intra-class correlations [79] based on the LLI for each ROI and task for general inter-rater agreement instead of Kappa coefficients or Cramers V for pairs of raters.

Results

Right-handed controls

Initial inspection of the fMRI images revealed, that one male right-handed participant showed right language dominance in all tasks. In another female right-handed participant, there were indications of partial crossed language dominance. These two participants were excluded from further analysis and will be described in the next section. For the remaining 11 participants, percentages of participants with significant activity in the selected VOIs, percentage signal change relative to the control task and corresponding z-scores separated for the three tasks are given in **Table 3**. **Figure 1** depicts the amount of activation in the VOIs considered as potential essential language areas as a function of language task. A representative example of a typical left-hemisphere language dominant participant is given in **Figure 2 A**.

The opercular part of the inferior frontal gyrus was activated in all participants by the sentence and synonym task (100%), while the rhyme task activated this area in 73% of the participants. The triangular part of

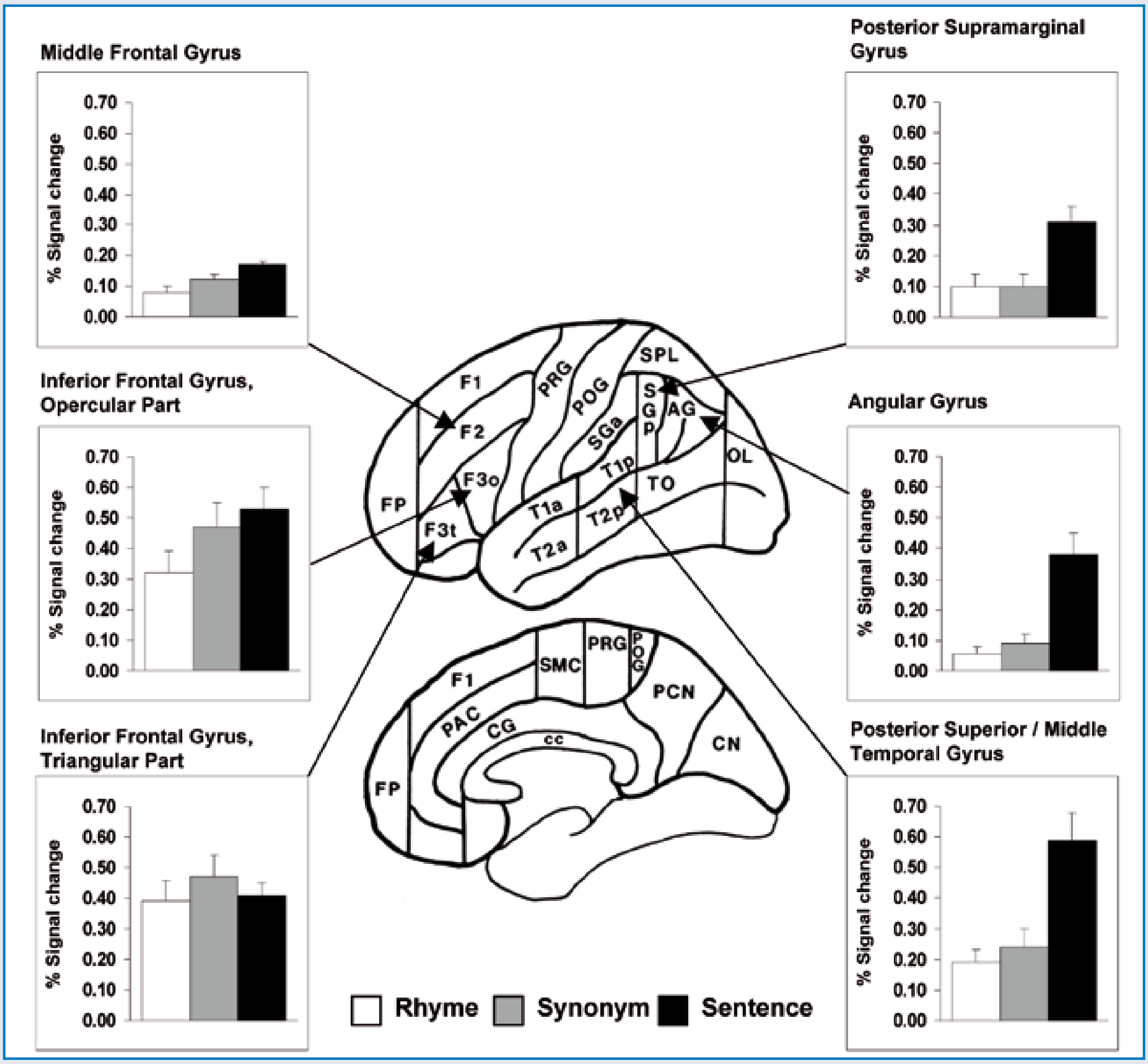

Figure 1: The schematic drawing in the centre shows the anatomically defined volumes of interest (VOI), adapted from the parcellation scheme described and depicted in Rademacher et al. ([75], abbreviations see text and Table 3).]The associated graphs depict the amount of activation the VOIs considered as potentially essential language areas as a function of language task (rhyme, synonym, sentence, with the letter task as control). The amount of activation is defined as group average of percentage BOLD signal change. The error bars represent the standard error of the mean. Note: The posterior superior and middle temporal gyrus (T1p, T2p) were combined to one VOI due to nearly identical activation in both VOIs.

the inferior frontal gyrus was activated to the same degree by all tasks (82%), while the middle frontal gyrus was significantly activated in 73% of the participants by the sentence task. The posterior superior and middle temporal language area were activated in all participants by the sentence task (100%), in 64% by the synonym, and in 55% by the rhyme task.

None of the putative non-essential language VOIs were activated by the sentence task with the exception of visual areas in some of the participants (lateral occipital gyri: 55%, cuneus: 64%). BOLD correlates in the supplementary motor cortex were found in 55% of the participants during the synonym and rhyme task.

According to a repeated measures ANOVA accuracy scores were statistically not different between the activation tasks ($p > 0.05$; mean ± Std: rhyme: 84.3±7.1; synonym: 91.4±3.2; sentence: 84.6±9.7. The mean accuracy score of the letter control-task was 94.2±2.7. Accuracy scores of the activation tasks did not correlate ($p< 0.05$; Bonferroni corrected) significantly to fMRI activations in none of the VOIs.

Left-handed controls and atypical language dominance

Two of the eight left-handed participants showed right-hemispheric language dominance, one bilateral

Table 3: Analysis of volumes of interest in healthy right-handers (n=11) with left hemisphere language dominance (shaded VOIs are considered as putative essential language areas). Note: The anterior/posterior superior and middle temporal gyrus as well as the paracingulate and cingulate cortex were combined to single VOIs because nearly identical activation in these VOIs.

Volume of interest (VOI)	Percentage of participants with significant activity in the VOI*			Percentage signal change relative to the control task (mean±std)			z-score (mean±std)		
	Rhyme	Synonym	Sentence	Rhyme	Synonym	Sentence	Rhyme	Synonym	Sentence
Frontal lobe									
FP, frontal pole	-	-	-	0.10±0.15	0.22±0.21	0.10±0.10	0.99±1.50	2.59±2.49	1.06±1.19
F1, superior frontal gyrus	-	-	-	0.03±0.06	0.02±0.03	0.06±0.12	0.22±0.45	0.24±0.44	0.47±0.80
F2, middle frontal gyrus	-	-	73	0.08±0.07	0.12±0.07	0.17±0.04	1.06±0.91	1.39±0.99	2.10±0.61
F3o, inferior frontal gyrus, opercular part	73	100	100	0.32±0.23	0.47±0.26	0.53±0.22	3.30±2.30	5.52±3.35	5.35±2.39
F3t, inferior frontal gyrus, triangular part	82	82	82	0.39±0.24	0.47±0.21	0.41±0.22	4.10±2.57	4.66±2.28	3.77±1.96
PRG, precentral gyrus	64	-	-	0.14±0.09	0.09±0.09	0.11±0.11	2.34±1.64	1.26±1.41	1.49±1.60
SMC, supplementary motor cortex	55	55	-	0.16±0.14	0.27±0.16	0.15±0.15	1.61±1.39	2.29±1.41	1.25±0.94
Temporal lobe									
T1a/T2a; anterior superior/middle temporal gyrus	-	-	-	0.04±0.05	0.12±0.11	0.23±0.24	0.47±0.64	1.51±1.44	2.95±3.28
T1p/T2p; posterior superior/middle temporal gyrus	55	64	100	0.19±0.12	0.24±0.20	0.59±0.32	2.60±1.90	3.05±2.70	4.18±2.14
TO, temporo-occipital cortex	-	-	-	0.03±0.05	0.00±0.00	0.02±0.03	0.47±0.79	0.01±0.01	0.23±0.39
Parietal lobe									
POG, postcentral gyrus	-	-	-	0.09±0.08	0.03±0.03	0.03±0.02	1.25±1.41	0.39±0.30	0.46±0.34
SPL, superior parietal lobule	-	-	-	0.04±0.09	0.01±0.02	0.10±0.07	0.43±0.94	0.09±0.22	0.66±0.52
SGa, anterior supramarginal gyrus	-	-	-	0.02±0.04	0.02±0.04	0.02±0.03	0.36±0.85	0.25±0.58	0.24±0.48
SGp, posterior supramarginal gyrus	-	55	73	0.10±0.12	0.10±0.12	0.31±0.18	1.63±1.92	1.68±1.92	3.70±1.88
AG, angular gyrus	-	-	82	0.06±0.05	0.09±0.11	0.38±0.22	0.77±0.73	1.47±2.11	4.49±2.70
PCN, precuneus	-	-	-	0.01±0.03	0.03±0.04	0.12±0.12	0.21±0.48	0.41±0.62	1.33±1.19
Occipital lobe									
OL, occipital lateral gyri	-	-	55	0.05±0.08	0.10±0.04	0.18±0.11	0.52±0.71	1.35±0.55	2.08±1.29
CN, cuneus	-	-	64	0.06±0.11	0.12±0.09	0.25±0.20	0.51±1.02	1.19±0.89	2.28±1.51
Medial paralimbic cortices									
PAC/CG, paracingulate/cingulate cortex	-	-	-	0.10±0.13	0.15±0.21	0.02±0.06	1.23±1.27	1.86±2.97	0.19±0.58

*Only percentages > 50% are given

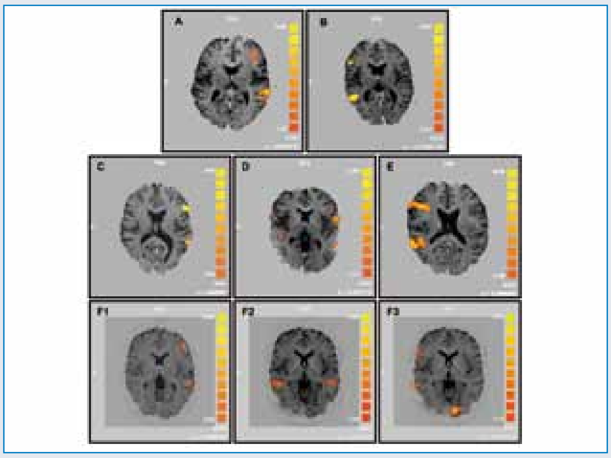

Figure 2: Representative examples of activation maps in healthy participants. (A,B) right-handers with left-hemispheric (A) and right-hemispheric (B) language dominance in the sentence task; (C,D,E) left-hander with left-hemispheric (C), bilateral (D), and right-hemispheric language dominance (E) in the sentence task; (F1-3) partial crossed language dominance in a right-hander with left-hemispheric language dominance in phonological processing (rhyme vs. letter task), F1), bilateral activation in semantic processing (synonym vs. rhyme task, F2) and right-hemispheric dominance in syntactic processing (sentence vs. synonym task, F3)

As mentioned before, two of the 13 right-handers showed atypical language dominance, one with right-hemispheric language dominance (see **Figure 2 B**). Another right-handed participant seemed to have a partially crossed language dominance: phonological and semantic aspects of language seemed to be processed with the left hemisphere, while syntactical aspects of language seemed to be processed with the right hemisphere (see also [80]). Therefore, we contrasted higher with lower order tasks (see **Table 2**), i.e. the rhyme to the letter (isolating phonology), the synonym to the rhyme (isolating semantic), and the sentence to the synonym task (isolating syntax). These contrasts showed left-hemispheric activations in phonological processing (**Figure 2 F1**), bilateral activation in semantic processing (**Figure 2 F2**) and right-hemispheric dominance in syntactic processing (**Figure 2 F3**).

Patients

Since the activations of the rhyme task revealed less constant BOLD signal increases in healthy right handed controls compared with the other tasks, in the clinical fMRI study this task was not used to shorten patients scanning time.

Table 4: Intra-class correlations for interrater agreement

Region of interest	Synonym		Sentence	
	Correlation	F(19,57)	Correlation	F(19,57)
Superior frontal gyrus	.57	2.4	.55	2.2
Middle frontal gyrus	.67*	3.0	.78*	4.6
Broca's area	.96*	23.1	.90*	10.1
Wernicke's area	.97*	30.3	.93*	15.3
Inferior parietal lobe	.70*	3.7	.61*	2.8
Precuneus / cuneus	.71*	3.4	.75*	3.8

*$p < 0.05$ (Bonferroni corrected, corresponding to $p < 0.004$)

language dominance and the others (5/8) typical left-hemispheric dominance (see **Figures 2 C-E** for representative examples).

According to a repeated measures ANOVA mean accuracy scores in left-handers were statistically not different between the activation tasks ($p > 0.05$; rhyme: 85.1±4.9; synonym: 89.1±1.6; sentence: 83.1±8.3) and were comparable to right-handers. The accuracy score of the letter control task was 93.8±3.7.

Visual rating

To evaluate interrater agreement of the four raters we calculated intra-class correlation coefficients [79] based on the LLI for each ROI and each task. Intra-class correlation coefficients and F-statistics (testing the null hypothesis of no agreement) are given in **Table 4**. With one exception for the superior frontal gyrus, all correlation coefficients were significant with excellent interrater agreement of r ≥.90 for the

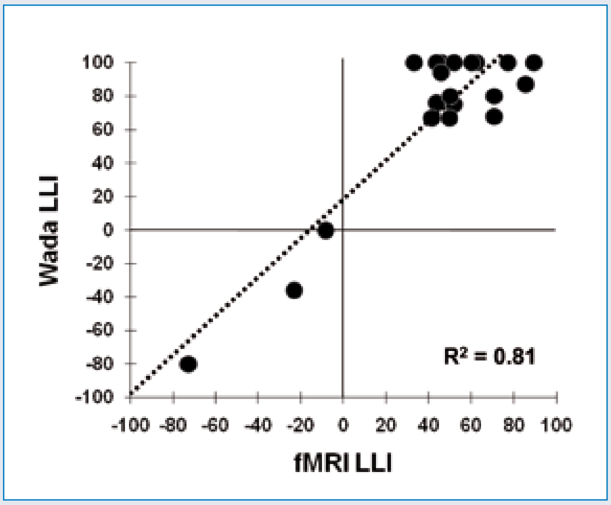

Figure 3: Wada LLI plotted against fMRI LLI for the best predicator, i.e. the combined ROIs of Broca's and Wernicke's area and both tasks (synonym, sentence). The regression function, y = 1.162x + 18.3, is shown as dashed line. The correlation coefficient is 0.90.

classical Broca's and Wernicke's language area. Interrater agreement was lower for the other putative essential language areas ranging from .61 to .78 in the inferior parietal lobule and middle frontal gyrus.

Concordance of Wada-test and fMRI

Since interrater agreement was very high, the LLIs of the four raters were averaged to calculate correlations between the Wada-test LLI and fMRI LLI separate for all the ROIs and each task-comparison. To evaluate whether combined scores across ROIs or tasks yielded better concordance between the Wada-LLI and fMRI-LLI compared to single ROI analysis, the following scores were calculated: (1) average of the classical Broca's and Wernicke's area separate for and averaged over both tasks; (2) average of all putative essential language areas, i.e. the middle frontal gyrus, Broca's and Wernicke's area and the inferior parietal lobe separate for and averaged over both tasks.

Correlation coefficients are given in **Table 5**. Highly significant correlations between the Wada- and fMRI-LLIs were observed for Broca's and Wernicke's area for both tasks, and both tasks combined ranging from .82 - .88. Although partially still in a high range (.52 - .71) correlations between the Wada LLI and activations in the inferior parietal lobe were not significant. None of the correlations for the middle frontal gyrus (.46 - .50) or

Table 5: Correlation coefficients between the language laterality indices of the Wada-test and fMRI activations.

Region of interest (ROI)	Synonym	Sentence	Both tasks
Single ROIs			
• Superior frontal gyrus	.84*	.56	.82*
• Middle frontal gyrus	.47	.46	.50
• Broca's area	.88*	.84*	.88*
• Wernicke's area	.83*	.82*	.84 *
• Inferior parietal lobe	.71	.52	.64
• Precuneus / cuneus	.11	.02	.09
Combined ROIs			
• Broca's and Wernicke's area	.89*	.86*	.90*
• Middle frontal gyrus, Broca's area, Wernicke's area, inferior parietal lobule	.81*	.75*	.85*

*$p < 0.05$ (Bonferroni corrected, corresponding to $p < 0.002$)

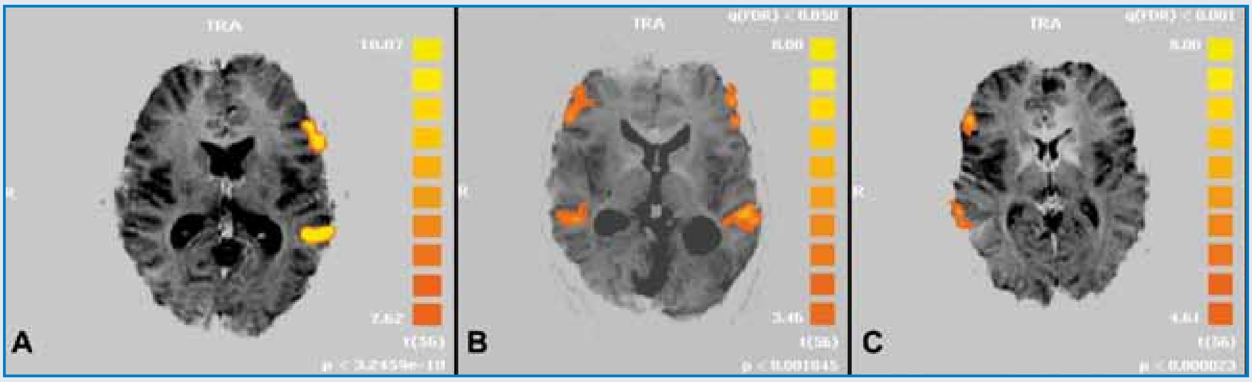

Figure 4: Representative examples of activation maps of three patients in the sentence task. (A) left-hemispheric language dominance (#16); (B) bilateral language dominance (#2); (C) right-hemispheric language dominance (#14).

the precuneus (.02 - .09) reached the critical level of significance. Finally, there were also significant correlations between the Wada LLI and activations in the superior frontal gyrus for the semantic task (.84), and both tasks combined (.82).

The best predictor of the Wada-LLI were activations in Broca's and Wernicke's areas averaged over both tasks (.90; see **Figure 3**), yet concordance rates separate for Broca's (.84 - .88) and Wernicke's area (.82 - .84) and separate for the synonym and sentence task were comparable. For all these variables fMRI and the Wada test was concordant in all cases in determining the hemisphere with greater language representation with no exception.

Seventeen patients had strong left hemispheric dominance for language as judged by the Wada test, with LLIs ranging from +67 to +100 (see **Table 1** and **Figure 3**) and fMRI, with LLIs ranging from +33 to +90. Three patients showed an atypical language distribution by the Wada test and fMRI. Wada LLIs in these patients ranged from -80 to 0, and corresponding fMRI LLIs ranged from -73 to -8.

Representative examples of activation maps of three patients with left, bilateral, and right hemispheric language dominance in the sentence task are given in **Figure 4**.

Sensitivity of the tasks to activate putative essential language areas

To evaluate sensitivity of the tasks to activate putative language areas we calculated percentages of patients with significant activations in the predefined ROIs. Data are summarized in **Table 6**. The sentence task showed the best sensitivity to activate putative essential language areas. Broca's (100%) and Wernicke's (100%) area were significantly activated by this task in all patients.

Accuracy scores

The data of three patients got lost because of a software problem. According to a t-test (dependent samples) accuracy scores of the synonym task (85.6±5.1) were significantly higher compared to the sentence task (78.3±7.1; $t(16) = 5.9$; $p < 0.001$). The mean accuracy score of the letter control-task was 92.0±4.9. Compared to right- and left-handed healthy controls (t-test, independent samples) accuracy scores were lower in patients both in the synonym ($t(34) = -3.5$; $p < 0.01$) and the sentence task ($t(34) = -2.09$; $p < 0.05$), while no such difference was found for the letter task ($p > 0.05$).

In patients, accuracy scores of the activation tasks did not correlate ($p < 0.05$; Bonferroni corrected) significantly to fMRI activations in none of the ROIs.

Discussion

Clinical fMRI studies are increasingly used as an additional tool in the assessment of patients who are candidates for resective surgery in eloquent areas of the brain. To warrant reliable results, fMRI studies have to ensure easy and reliable interpretation by the neuroimager and neurosurgeon in charge to plan resection. In addition, the time of scanning should be as short as possible to ensure patients' comfort and compliance. Finally, the selected paradigm must unambiguously provide an activation of putative essential language areas to provide comprehensive data about the lateralization and anatomical topology of the brain areas under investigation.

The study at hand demonstrated that the sentence task showed robust BOLD responses in putative essential language areas in right-handed healthy controls and patients. Activations were found in Broca's and Wernicke's area in all participants (100%). Additionally, the inferior parietal lobe and the middle frontal gyrus were activated in almost all right-handed controls and patients. Furthermore, none of putative non-essential

Table 6: Percentage of patients (> 50%) with significant activity in the region of interests

Region of interest (ROI)	Synonym	Sentence
• Superior frontal gyrus	70	75
• Middle frontal gyrus	80	90
• Broca's area	100	100
• Wernicke's area	95	100
• Inferior parietal lobe	75	85
• Precuneus / cuneus	–	–

language areas were activated by this task with the exception of visual associated cortical areas in about half of the healthy right-handers and the superior frontal gyrus including the SMA in 75% of the patients. This indicates on the one hand that the visual demands of the sentence task are experimentally not fully balanced compared to the letter control task, and on the other hand that the sentence tasks need more intensive articulatory planning and articulatory execution (e.g. [81]) compared to the letter control task.

One limitation of this study is the relative small sample size. However, our results re-confirm an obser-vation derived from a variety of different language paradigms (see **Table in the appendix**) that inferior frontal activation occurs reliably and constitutes a good marker of language lateralization. What appears to be new in this study (and in the validation literature in general) is the universal activation of the frontal opercular region in particular, probably reflecting the syntactic components of the sentence task (for a review and critical discussion of this aspect see [82]). Additionally, the posterior temporal language region was also universally activated in controls and patients by the sentence task. However, the activations in this study did not go substantially beyond previously reported anterior and posterior markers of language lateralization and did not activate other putative essential language areas like the anterior temporal language areas. It seems that activations of these regions need other task designs (e.g. semantic audio-visual processing; (see Figure 3 of Vigneau et al. 2006 [82]).

The sentence task lateralized 11/12 (8%) right-handed, 3/8 (37%) left handed healthy participants, and 3/20 (15%) of the patients to the right hemisphere or showed bilateral activations. These rates in healthy right and left-handers are consistent with other studies [22, 36]. More importantly, our task allowed a correct classification of patients with atypical language dominance, which has to be considered in the presurgical evaluation of patients with epilepsy, particularly after early brain injury and left sided medial lobe epilepsy and reaches about 25% [19, 21, 37, 45, 49, 83]. The slightly lower incidence rate of 15% atypical language dominance in our patients may be due to the fact, that we incorporated eight patients with brain tumours. Also important, there was full concordance between the Wada Test and the fMRI tasks in determination of the language dominant hemisphere. Our task allowed a correct classification of all patients, even those with atypical language dominance.

One right-handed (handedness laterality +100) healthy participant showed partial crossed language dominance with left-hemispheric language dominance in phonological processing, bilateral activation in semantic processing, and right-hemispheric dominance language in syntactic processing (**Figure 2 F1-3**). She is a well functioning person with a high academic level and known familial sinistrality and ambidexterity (her father, a surgeon was famous to operate with equal dexterity with the left or right hand). She has no history of difficulties while delivery, development or any neurological or psychiatric problems. Detailed anatomical MR analysis gave no hints of cerebral pathology. Thus, partial crossed language dominance, i.e. interhemispheric dissociation of language functions not only seems to be a phenomenon in chronic epilepsy [84-88] but also a genetic variability in healthy individuals. While the Wada Test only gives an index of language laterality, it does not localize specific language abilities; fMRI paradigms have this ability and the ability to indicate partially crossed language dominance as demonstrated with our right-handed healthy participant.

A practical goal of this study was to test whether the sentence task can be used in clinical routine. A simple clinical rating procedure of language lateralization was performed by different neuroimagers. Additionally, we were interested how good this clinical rating corresponded to the LLI of the Wada test. Since fMRI activation heavily depends on the capability of an individual to perform a task (cf. [78]), no constant activations were used for the visual ratings. In contrast to previous studies that investigated visual ratings of language lateralization [44, 48-50] we used a graded rating (1=no, 2=slight, 3=moderate, 4=strong) of BOLD correlates in predefined eloquent cortical areas allowing us to calculate intra-class correlations for general interrater agreement. Interrater reliability between the four raters was very good for classical Broca's and Wernicke's area with highly significant intra-class correlations ranging from .90 to .97. Intra-class correlations were also significant for the other essential or non-essential language areas, i.e. the inferior parietal lobe, the middle frontal gyrus and the precuneus/cuneus ranging from .61 to .78.

Interrater concordance in this study was higher compared to other studies that used a clinical rating system [44, 48-50] except from the study of Gaillard and co-workers [50]. In that study, however, a panel of

Appendix. Studies comparing the Wada test with fMRI of language

Tasks Study	Year	n[a]	Wada			fMRI						Concordance		Discordance[b]
			L	R	B	Probe: Stimulus-Response	Control	Behavioral monitoring	ROI	Regions activated[c]	Quantification	%	r	
Verbal fluency														
Adcock [38]	2003	19	15	1	3	Letter-Words	Rest	No	Whole brain excluding occipital cortex and CER	Different regions activated for left and right TLE patients	LLI(±26.5)	89%	-	B: 11%
Bahn [55]	1997	7	5	2	0	Letter-Words Noun-Rhyme	Rest Rest	No No	Br (F3o), We (post T1), post F2, Caudate, SMA	Br, post F2, SMA, We, Caudate	CR	43-86%[d]	-	B: 14%
Bazin [51]	2000	7	6	1	0	Semantic category-Exemplifiers	Rest	No	F3, F2, F1, SMA, T1, T2/T3, PAR, PCN	F3, F2, SMA, PAR, F1, T1, PCN, T2/T3	LLI(±100)	100%	0.85-0.94[e]	-
Benson [56]	1999	12	9	2	1	Noun-Verbs	Rest	No	Whole brain	ng	LLI(±100)	100 %	-	-
Chlebus [52]	2007	15	12	3	0	Letter-Words	Rest	No	Whole brain, anterior two-thirds of the hemispheres (ATT), lateral ATT, lateral PFC, Br, SMA, CER	F3, F2, F1, CER, SMA, T2, T3, HIPP, SPL	LLI(±100)	33-100%[f]	0.64-0.94[f]	-
Deblaere [39]	2004	17	15	0	2	Word-Wordchain	Motor	No	Whole brain, FRON (F1,F2), TP (post T1,T2, SG, AG)	F3, F2, F1, T2, SG, AG, THAL	LLI(±20)	88-100%[g]	-	-
Hertz-Pannier [57]	1997	6	5	0	1	Letter-Words Semantic category-Exemplifiers	Rest Rest	No No	F3, F2, F1, CING, TEMP	F3, F2, F1	LLI(ng)	66-83%[h]	-	B: 17%
Liegeois [40]	2002	4	1	2	1	Noun-Verbs	Rest	No	F1	ng	LLI(±20)	100%	-	-
Sabbah [41]	2003	20	12	8	0	Letter-Words Semantic category-Exemplifiers	Rest Rest	No No	Whole brain	F3, F2, F3, PRG, POG, SMA,T1,T2,T3	LLI(±20)	95%	-	R: 5%
Woerman [48]	2003	94	71	ng[i]	ng[i]	Letter-Words	Rest	No	Whole brain	FRON lateral (100 %) Temporo-posterior (74 %), PAR (80%), FRON mesial (51 %)	CR (0.86)	91%	-	A[i]: 3% L: 6%
Worthington [54]	1997	9	ng	ng	ng	Letter-Words	Rest	No	ng	ng	CR	55%	-	ng[j]
Yetkin [53]	1998	13	12	1	0	Letter-Words	Rest	No	F3,PRG	F3,PRG, SMA, CING	LLI(±100)	92%	0.93	R: 8%
Semantic decision / lexical retrieval														
Baciu[k] [42]	2005	10	8	0	2	Nouns – living?	Rest	No	FRON (BA44-47), TP (BA21,22,37,40)	ng	LLI(±15, ±20, ±25,)	50-60%[k]		L: 40%
Benke [49]	2006	68	54	6	8	Nouns-Supermarket and less than 7 €?	Perceptual	Yes	FRON (F3,F2,F1), TP (T1,T2,T3,AG,SG)	FRON, TP, SPL, PCN	CR (0.36-0.72)	68-78%[l]	-.	L: 9% B: 12% R: 1 %
Binder [7]	1996	22	18	1	3	Animal names – USA? Commonly used by humans?	Perceptual	Yes	Whole brain	F3, F2, PRG, F1, AG, post T3, TF, T2,	LLI(±100),	100%	0.96	-
Desmond [12]	1995	7	4	3	0	Nouns-concrete/ abstract?	Perceptual	Yes	F3	F3t, FOC, ant F2, F3, CING	LLI(±100)	100 %	-	-
Fernandez [59]	2001	6	5	ng	ng	Noun pairs.-synonym?	Perceptual	Yes	Br, PFC outside Br, TP	post T1, SG, AG, F3, F2, F1, T2, CING	LLI(±100), CR	100%	-	-
Spreer [43]	2002	21	16	4	1	5 Nouns – synonym pair?	Visual	Yes	Whole brain, FRON, TP	FRON, TP, and others, not further specified	LLI(±20)	76-86%[m]	-	L: 10 % R: 4 %
Gaillard [44]	2002	18	14	2	2	Object description -naming	Perceptual	No	F3, F2, WE defined as T1, T2, IPL	As ROIs, other not given	LLI(±20) CR (0.77-0.82)	72-83%[n]	-	L: 6% B: 11%
Phonological decision														
Baciu [60]	2001	8	7	0	1	Word pairs-rhyming?	Perceptual	No	F1 ,post T1, IPL, PFC, PMC	F3, T1, IPL, F2, T3, PMC, CING, Insula, middle occipital gyrus, SPL	CR	100%[o]	-	-
Panel of tasks														
Arora [45]	2009	40	29	4	7	*Verbal fluency:* Letter-Words Semantic category-Exemplifiers *Semantic-syntactic decision:* Reading/hearing sentences-Semantically-syntactically correct?	Perceptual Perceptual Perceptual	? ?	Whole brain, and whole brain excluding midline activations	ng	LLI(±10)	65-79%[p]	-	R: 3% B: 18%
Carpentier [61]	2001	10	8	2	0	*Semantic-syntactic decision:* Reading / hearing sentences -Semantically / syntactically correct?	Perceptual	?	Whole brain, Br (BA44,45), We (BA22)	Reading: SG, We, TF, Br, PRG, SMA Hearing: We, Br	LLI(±100)	40-90%[q]	-	L: 10%
Gaillard [50]	2004	25	22	2	1	*Verbal fluency:* Letter-Words Semantic category-Exemplifiers *Naming:* Reading / hearing object description -naming *Reading / listening:* Reading / listening to stories- no response	Rest Rest Perceptual Perceptual	No No No No	Whole brain	ng	CR (single tasks: 0.60-0.86; all tasks 0.91-1.0)	84%[r]	-	L: 12% B: 4%
Lehericy [46]	2000	10[s]	9	0	1	*Verbal fluency:* Semantic category-Exemplifiers *Repetition* Sentence-repetition *Listening:* Listening to stories- no response	Rest Rest Perceptual	No No No	FRON, F3, F2, F1, SMA, CING, INS, TEMP, TP, T2/T3, SPL, PCN	Verbal fluency: FRON, F3, ant INS, F2, SMA, CING, TP Repetition: No lateralized activation Listening: TP, F2, SMA, CING, F1, F3	LLI(±25)	80-90%[s]	0.62-0.89[s]	B: 10%

Tasks														
Study	Year	n[a]	Wada			fMRI						Concordance		Discordance[b]
			L	R	B	*Probe:* Stimulus-Response	Control	Behavioral monitoring	ROI	Regions activated[c]	Quantification	%	r	
Panel of tasks (continued)														
Rutten [47]	2002	18	11	3	4	*Verbal fluency:* Letter-Words Noun-Verbs *Naming:* Object drawings-naming *Listening:* Listening to sentences-no response	Rest Perceptual Perceptual Perceptual	No[u] No[u] No[u] No	F2, F3, T1, T2/T3, AG, SG	Not given for separate tasks; for all tasks combined F3, F2, AG, SG	LLI(±25)	50-82%[u]	-	L:6% R:6% B:6%
Summary	All studies; For complete data:	486 377	368 (76%)[v] 292 (78%)	47 (10%)[v] 47 (12%)	38 (8%)[v] 38 (10%)						Mean: Std.: Range:	88.9% 11.9 55-100%	Mean[w]:	L: 2.5%[x] R: 1.2% B: 4.5%

[a] The n includes only those with valid Wada tests and fMRI.

[b] Percentages of discordance between Wada test and fMRI are given for the best concordance score separately for left-, right or bilateral language dominant patients according to Wada test.

[c] In descending order – when possible – from putative language-essential to putative language-non-essential regions (for a description of putative language-essential regions see introduction).

[d] There was no difference between tasks. Concordance between Wada test and fMRI varied by ROI: Br 86%, F2 71%, SMA 71%, We 43%, Caudate 43%.

[e] Correlations between Wada test and fMRI varied by ROI and were significant for all ROIs together (r=0.85), all frontal lobe ROIs (r = 0.94) and F2 (r=0.88).

[f] Concordance and correlations between Wada test and fMRI varied by ROI. Highest concordance (100%) and correlations (r=0.94) were found for Br.

[g] Concordance between Wada test and fMRI varied by ROI. Highest concordance was found for whole brain (100%), the FRON- (88%) and the TP-ROI (88%).

[h] Concordance between Wada test and fMRI varied by ROI: F2 83%, F3 66%, F1 66%, F1-F3 together 83%.

[i] Twenty-nine patients had atypical language dominance, but it was not specified if dominance was right or bilateral; also, 100 patients had valid Wada test, but six had invalid fMRI.

[j] Exact data are not given. It is reported, that in 3/9 cases there was a disagreement between Wada test and fMRI, and in one case the Wada test showed bilateral language functions, while fMRI was lateralized.

[k] In this study 35 patients were tested. Four tasks were used, however not performed in all patients. Wada test was also not performed in all patients. Thus, we only report the results of a semantic decision task where most of the Wada tests were available. Concordance between Wada test and fMRI varied by ROI.

[l] Concordance between Wada test and fMRI varied by ROI: FRON 78%, TP 69%, FRON and TP combined; 68%.

[m] Concordance between Wada test and fMRI varied by ROI: Whole brain 76%, FRON 86%, and TP 81%.

[n] Concordance between Wada test and fMRI varied by ROI and rater (n=3): ROI 83%, Rater1 83%, Rater2 72%, Rater3 83%.

[o] Concordance between Wada test and fMRI is based on clinical rating of all ROIs (whole brain).

[p] Data were analyzed separately for left or right lateralized and for bilateral lateralized patients. With respect to lateralized patients concordance between Wada test and fMRI were 77% for word fluency, 84% for the reading task, 83% for the hearing task, and 91% for all tasks. Bilateral patients showed great discrepancies between the Wada test and fMRI. For reasons of comparison with the other studies data are given for the whole group. LLI were also calculated for whole brain with excluding midline activations with higher concordance between Wada test and fMRI. Concordance between Wada test and fMRI varied by task and determination of LLI. Whole brain: reading sentences: 68%, hearing sentences: 70%, word fluency: 65%; all tasks: 71%. Whole brain excluding midline structures: reading sentences: 74%, hearing sentences: 73%, word fluency: 74%; all tasks: 79%.

[q] Concordance between Wada test and fMRI varied by task and ROI. Whole brain: reading sentences: 80%, hearing sentences: 40%, both tasks: 80%. Br and We: reading sentences: 90%, hearing sentences: 80%, both tasks: 90%.

[r] Concordance between Wada test and fMRI are only given for all tasks combined.

[s] Wada LLIs were calculated separately for language production, language comprehension and all tasks together. For reasons of comparison with the other studies data are given for global Wada LLIs. Concordance between Wada test and fMRI are only given for the frontal LLI of the verbal fluency task (80% concordance) and the temporal LLI for the story listening task (90% concordance). Correlations between Wada test and fMRI varied by ROI and task (17 correlations are reported). Also linear regression coefficients for verbal fluency and frontal activations (R^2=0.772) and for the listening task with temporal activations

(R²=0.09) are given.

u Behavioral monitoring was performed before the actual scan session. Concordance between Wada test and fMRI varied by task and ROI. Combined tasks, all ROIs: 83%; verbal fluency, all ROIs: 72%; combined tasks, frontal ROIs: 67%; combined tasks, temporo-parietal ROIs: 50%.

v Note that in 3 studies (Fernandez et al., 2001; Woerman et al., 2003; Worthington et al., 1997) data with respect to language dominance were either not given or in the cases of right- or bilateral dominance summarized as atypical language dominant. Comparing only typical (left) and atypical hemispheric language dominance 76% of the 486 patients showed typical and 23% atypical hemispheric language dominance.

w Note that the percentage of the discordance rates do not fully add to 100% to the percentage of the concordance rates, because in some studies discordance data are not given.

x We excluded the study by Baciu et al., 2005, because the high discordance score of left language dominant patients is biased by an extreme score of 40% of only 8 patients in this study.

Abbreviations (anatomical abbreviations according to [75]). A Atypical language dominance (i.e. right- or bilateral language dominance); *AG* angular gyrus, ant anterior, *B* Bilateral-hemispheric language dominance, *BA* Brodman's area, *Br* Broca's area, *CER* Cerebellum, *CING* Cingulate, *CR* Clinical rating (in brackets interrater agreement, when given), *fMRI* functional magnetic resonance imaging, *F1* superior frontal gyrus, *F2* middle frontal gyrus, *F3* inferior frontal gyrus, *F3o* inferior frontal gyrus, opercular part, *F3t* inferior frontal gyrus, triangular part, *FOC* frontoorbital cortex, *FRON* Frontal lobe HIPP Hippocampus, *INS* insula, *IPL* inferior parietal lobule *L* Left-hemispheric language dominance, *LLI* Language laterality index (usually computed as (L-R)/(L+R)*100, with *L* and *R* are activations for the left and right hemisphere; this yields LLIs ranging between +100 (strong left hemisphere dominance) to -100 (strong right hemisphere dominance; in brackets: ±100 means, that no cut off score was used, instead language laterality is considered as a continuum; ±n means, that LLIs were classified as left hemisphere dominant (defined as LLI > +n), bilateral (-n ≤= LLI ≤ +n) or right hemisphere dominant (defined as LLI < -n), *ng* not given, *PAR* Parietal lobe, *PCN* Precuneus, *PFC* prefrontal cortex, *PMC* premotor cortex, *POG* prostcentral gyrus, *PRG* precentral gyrus, post posterior, *r* correlation (between quantitative laterality indexes of Wada-Test and fMRI), *R* Right-hemispheric language dominance, *ROI* Region of interest, *SG* supramarginal gyrus, *SMA* supplementary motor area, *SPL* superior parietal lobule, *T1* superior temporal gyrus, *T2* middle temporal gyrus, *T3* inferior temporal gyrus, *TEMP* Temporal lobe, *TF* temporal fusiform gyrus, *THAL* Thalamus *TLE* temporal lobe epilepsy, *TP* temporo-parietal region (usually including the posterior temporal and inferior parietal lobe), *We* Wernicke's area

tasks targeting different aspects of language processing was used with similar results compared to our single sentence task approach. Our study showed that one fMRI task that integrates phonology, semantic and syntax, that is the main components of language processing, depicts typical and atypical language dominance and BOLD correlates of all essential language areas.

Taken together, clinical visual analysis of fMRI activations with a single sentence task offers an alternative to assess language dominance and localization of language areas in the individual. In our cohort, the visual determination of language dominance was comparable to other studies using quantitative procedures (see [44]). The graded clinical ratings scale of predefined brain areas offers an additional value since activated regions known not to be of interest of language mapping can simply be ignored [45].

The added clinical value of fMRI today seems to be increasingly important for accurate language localization in lesional surgery and resective surgery close to eloquent brain areas. In this context, the Wada Test is no longer necessary since it provides an index of language laterality, but ignores specific language localization. The data presented in this study may provide additional insights that fMRI of language is also capable as a complementary tool to intraoperatively direct cortical stimulation in brain lesions located in language areas (for a review see [89]).

In summary, we have demonstrated that a single sentence task as proposed in this study reliably lateralizes language and activates putative essential language areas. Moreover, a visual interpretation of the fMRI activation maps by clinical neuroimagers has shown to be comparable to quantitative procedures for the determination of language dominance. This is of special relevance under clinical conditions, when patients with brain tumours or candidates for epilepsy surgery are under evaluation for surgery. Performing visual ratings of the sentence task as proposed in this study instead of a whole language test battery may help to make clinical fMRI more economic, optimize patients comfort by reducing the time of the examination, and maintain reliable data interpretation for clinical neuroimagers and neurosurgeons.

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