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N.B.: When citing this work, cite the original article.

Original Publication:

Helene M van Ettinger-Veenstra, Mattias Ragnehed, Mathias Hällgren, Thomas Karlsson,  
Anne-Marie Landtblom, Peter Lundberg and Maria Engström, Right-hemispheric brain  
activation correlates to language performance, 2010, NEUROIMAGE, (49), 4, 3481-3488.

<http://dx.doi.org/10.1016/j.neuroimage.2009.10.041>

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Postprint available at: Linköping University Electronic Press

<http://urn.kb.se/resolve?urn=urn:nbn:se:liu:diva-53932>

# Right-hemispheric brain activation correlates to language performance

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**Running title:** *Brain lateralization, dichotic listening and fMRI*

## **Abstract**

Language function in the right-hemispheric homologues of Broca's and Wernicke's areas does not only correlate with left-handedness or pathology, but occurs naturally in right-handed healthy subjects as well. In the current study, two non-invasive methods of assessing language lateralization are correlated with behavioral results in order to link hemispheric dominance to language ability in healthy subjects.

*Functional Magnetic Resonance Imaging* (fMRI) together with a sentence-completion paradigm was used to determine region-specific lateralization indices in the left- and right-sided Broca's and Wernicke's areas, the frontal temporal lobe, the anterior cingulate cortex and the parietal lobe. In addition, *dichotic listening* results were used to determine overall language lateralization and to strengthen conclusions by correlating with fMRI indices. Results showed that fMRI lateralization in the superior parietal, the posterior temporal, and the anterior cingulate cortices correlated to dichotic listening. A decreased right ear advantage (REA), which indicates less left-hemispheric dominance in language, correlated with higher performance in most administered language tasks, including reading, language ability, fluency, and non-word discrimination. Furthermore, right hemispheric involvement in the posterior temporal lobe and the homologue of Broca's area suggests better performance in behavioral language tasks. This strongly indicates a supportive role of the right-hemispheric counterparts of Broca's and Wernicke's areas in language performance.

## **Introduction**

Knowledge about the lateralization of brain functions is important for resolving both research and clinical issues. An increasing interest in lateralization is presently seen, among others, in research on schizophrenia (Angrilli et al., 2009; Bleich-Cohen et al., 2009) and dyslexia (Pernet et al., 2009). In language research, the lateralization of language function can be used to explain subtle differences in behavior and cognitive skills. For example, clinical language lateralization assessment is necessary in the examination of epilepsy patients prior to resective surgery of the temporal lobe. The standard method to determine language laterality in the clinic is the Wada procedure, which is highly invasive, with associated risks for the patient (Baxendale, 2009).

Non-invasive alternatives to the Wada test have proven to be reliable in determining lateralization of language function in the brain. Lateralization in healthy subjects is often determined by a dichotic listening test, where ear dominance is correlated to language dominance. This is based on the notion that the contralateral (direct) pathways from the ears to the opposite hemisphere are stronger than the projection to the ipsilateral hemisphere (Kimura, 1961; Geffen et al., 1978). Typically, language is left-lateralized, resulting in a better perception of verbal stimuli in the right ear compared to the left, expressed in degree of right ear advantage (REA) (Hugdahl, 1995).

A more recent, promising method is the use of functional Magnetic Resonance Imaging (fMRI) to determine language lateralization, enabling language function location within the hemispheres. With fMRI, the hemispheric asymmetry of the activation pattern reflects lateralization of language. The fMRI-determined lateralization index (*LI*) has been shown to correlate with some versions of dichotic listening (Fernandes et al., 2006; Fontoura et al., 2008; Van den Noort et al., 2008). More convincingly, both dichotic listening (Strauss et al., 1987; Hugdahl et al., 1997; Fontoura et al., 2008) and fMRI-*LI* tests (Desmond et al., 1995; Yetkin et al., 1995; Spreer et al., 2002, Fontoura et al., 2008) repeatedly show a correlation with Wada test results. However, fMRI-*LIs* are influenced by task choice (Lee et al., 2008) and are more robust when measured in regions of interest (ROIs) rather than when derived from a whole-brain index calculation (Spreer et al., 2002). In their study on language lateralization, Szaflarski and colleagues (2002) point out that fMRI-*LIs* depend on the locations from which the laterality is derived. They showed that frontal regions are more strongly linked to handedness and hence show a higher incidence of right-sided lateralization

for left-handed people, thus replicating results from Ellis and colleagues (1998). Such results strongly advocate a hypothesis-driven choice of ROIs in deriving *LIs*, rather than calculating whole-brain-laterality.

When fMRI results are used to estimate laterality the most common approach is to generate an activation map by imposing a pre-defined statistical threshold to declare voxels as active or inactive. The *LI* is often determined by simply subtracting and normalizing right-hemispheric activation from left-hemispheric activation. However, this index can be severely influenced by many methodological factors, such as activation thresholds and outlier influence. One possible way to circumvent the threshold problem is to calculate *LIs* for several different thresholds and then use a weighted average of the indices to define the resulting *LI*. In this study, a method presented by Wilke and colleagues (2006; 2007) was used. This method combines the weighted average approach with a bootstrap procedure to further increase the robustness of the *LI* calculation.

In determining fMRI-*LI* it is important to employ both a reliable *LI*-calculation method, as discussed above, and a language paradigm that activates areas of interest. Semantic sentence processing generally activates Wernicke's area and the angular gyrus whereas word generation relies on Broca's area (Price, 2000). The role of the inferior frontal lobe (specifically Broca's area) and the posterior superior temporal gyrus (Wernicke's area) in language processing is extensively researched and exceeds the straightforward view of a division between language accessing and production as summarized by Geschwind (Geschwind, 1965; Bookheimer, 2002; Price, 2000; Hickok and Poeppel, 2004). The frontal temporal lobe has been shown to be active during sentence reading (Fletcher et al., 1995), albeit not consistently (Price et al., 2003) and is involved in name retrieval (Damasio et al., 2004). Conventional word retrieval paradigms also trigger activation in the left temporal gyrus (Wise et al., 2001; Damasio et al., 2004). The anterior cingulate cortex shows activity during fluency paradigms (Lurito et al., 2000; Fu et al., 2001). Kircher and colleagues (2001) used fMRI to study sentence completion and found activation in the left middle frontal and anterior cingulate gyrus as well as in the superior parietal lobe (precuneus). Activation in the superior parietal lobe is also found during verb production (Shapiro et al., 2006) and suggested to be involved in retrieval of associations during semantic processing (Carreiras et al., 2009). We selected five regions of interest in primary language areas (the posterior temporal lobe and the inferior frontal lobe) and areas involved in cognitively demanding linguistic tasks (the frontal temporal lobe; the superior parietal lobe and the anterior cingulate

cortex). Next to their involvement in language, the ROIs were chosen so that they were well apart, in order to detect separate clusters of activation. For exploring language-related activation in the selected ROIs, a sentence completion paradigm, which involves semantic processing as well as word generation, was used (McDonald and Tamariz, 2002).

In the present study we wished to investigate language lateralization in correlation to language performance. Sentence completion has been shown to elicit activation in the right hemisphere, additional to the described left-hemispheric activation, specifically in the middle temporal gyrus (Kircher et al., 2001). The classical view on right-hemispheric contributions is the involvement in decoding ambiguity, metaphors and distant semantic relationships (Koivisto, 1997; Abdullaev and Posner, 1997; Chiarello, 1998). In addition, the contribution of the right hemisphere involves decisions about semantic relations between words (Faust, 1998; Beeman and Chiarello, 1998). Just and colleagues (1996) investigated the influence of the right hemisphere (right-sided counterparts of Wernicke's and Broca's areas) in language function employing an increased-demand fMRI paradigm. The authors found increased activation in right-hemispheric areas when cognitive demands were high. Likewise, Dräger and colleagues (2004) described increased activation in the right parietal lobe as a result of increased task difficulty.

The main aim of this study was to assess lateralization of language function using both dichotic listening and fMRI-based region-specific *LIs*, in order to clarify the usability of both methods in clinical lateralization assessment. Secondly, we aimed to apply these methods in order to determine the influence of language ability on the amount of (additional) right-hemispheric activation. We correlated fMRI and dichotic listening derived *LIs* with performance measurements on tasks measuring fluency, reading ability, picture naming and high-level linguistic ability performance.

## ***Materials and Methods***

### *Subjects*

Sixteen healthy, right-handed subjects of different gender and age were recruited to participate in a series of behavioral tasks tapping language functions, an fMRI sentence completion paradigm, and a dichotic listening test. One subject was excluded due to movement artifacts in fMRI images and another subject was excluded due to hearing impairment, which could have confounded the dichotic listening result. Results from 14 subjects, 7 females and 7 males, aged 21–55 (mean age = 36.9, SD=11.7) years are presented in this study. Pre-experimental screening consisted of assessing handedness by means of the Edinburgh handedness inventory. In addition, MR-safety and health status were recorded. The subjects had neither a contraindication for MR safety, nor any history of neurological, cognitive or psychiatric disorders - including alcohol and drug abuse - or pathological language problems. Examination of the anatomical MRI images did not reveal any individual brain anomalies. The test procedure encompassed a total of 2 – 3 hours, distributed over 2 days. The study was approved by the regional Ethics Committee of Linköping and the subjects signed written informed consent.

### *fMRI acquisition and analysis*

Images were acquired using a Philips Achieva 1.5 T MR-scanner. The language paradigm was presented using high-resolution video goggles (Resonance Technology Inc., CA, USA). For experimental design and task presentation, Superlab Pro 4 software was used (Cedrus Corp., San Pedro, USA).

At the start of the fMRI examination the participants were given instructions regarding the language paradigm and were familiarized with the procedure. Functional images were acquired using a blood oxygen level dependent (BOLD) sensitive gradient echo sequence, employing the following acquisition parameters: TR = 2.7 s; TE = 40 ms; FOV = 24 cm; flip angle = 90°; matrix = 80 x 80 x 32; slice thickness = 3 mm. The slices were aligned between the floor of sella turcica and the posterior angle of the fourth ventricle.

The sentence completion paradigm was visually presented and consisted of four blocks of 8 sentences each, in which the last word was substituted by "...". The sentences were presented for 3 seconds, followed by an asterisk presented for 2 seconds. The subjects were instructed to think of one or several words that would complete the sentence during the time the asterisk

was on screen. Trial blocks were alternated with a total of 5 control blocks consisting of asterisks, mimicking a short sentence. These were presented for 3 seconds and followed by a single asterisk presented for 2 seconds. The subjects were instructed not to think of words or sentences during the control blocks. In addition, the subjects were randomly assigned to one of two paradigms each containing different sentences of an equal degree of difficulty. The order of the blocks and sentences within the blocks was random for each subject. The total duration of the test was 5 minutes.

The sentences were translated into Swedish from a Spanish study by McDonald and Tamariz (2002) and validated in-house using 29 native Swedish students, 55% female and 45% males, ranging between 19 and 37 years (mean age 23 years). Sentences with more than 10% irrelevant answers as well as sentences with marked gender differences were excluded.

SPM5 (<http://www.fil.ion.ucl.ac.uk/spm/software/spm5/>) was used for the analysis of the fMRI data. Functional scans were realigned to the first image of the time series, normalized at  $2 \times 2 \times 2 \text{mm}^3$  to a standard brain atlas (MNI space) and smoothed using an 8 mm FWHM Gaussian kernel. A general linear model (GLM) was fitted to the data and the estimated regression coefficients for each voxel were tested against zero with a t-test to generate individual statistical maps which were entered in the calculation of fMRI-LI. To create figure I, the group activation was assessed by a 2<sup>nd</sup> level one sample t-test. The group statistical map was thresholded using a false discovery rate (FDR) correction (Benjamini and Hochberg, 1995) to control for multiple comparisons across all voxels (significance threshold of  $p = 0.05$ ).

Five non-overlapping regions of interest (ROIs) were defined as:

- Frontal Temporal Lobe (FTL, middle and superior temporal gyrus)
- Posterior Temporal Lobe (PTL, middle and superior temporal gyrus)
- Inferior Frontal Gyrus (IFG) – opercular and triangular part corresponding with Broca's area
- Anterior Cingulate Cortex (ACC)
- Superior Parietal Lobe (SPL)

All ROIs were constructed using WFU\_Pickatlas software (version 2.4) (Maldjian et al., 2003). The ROIs were post-processed to be mirror-symmetrical in the left-right direction.

### *fMRI laterality index*

Lateralization was assessed by computing *LI* from the individual statistic images (T-maps). The commonly used approach (Eq. 1) takes only the number of activated voxels in the left or right hemisphere within an ROI in account.

$$LI = \frac{\sum Left - \sum Right}{\sum Left + \sum Right} \quad (1)$$

In this calculation  $\sum Left$  and  $\sum Right$  denote the number of activated voxels in each hemisphere or region of interest within each hemisphere. The *LI* ranges from -1 (only right-hemispheric activation) to +1 (only left-hemispheric activation). The main difficulty with this definition is that the resulting *LI* depends on the statistical threshold chosen to define activation. One way to avoid the threshold dependence is to calculate *LIs* for several different thresholds (defined by the t-statistic, *t*) and use a weighted average of the *LIs* to define the final *LI* (Eq. 2).

$$LI = \frac{\sum t * LI(t)}{\sum t} \quad (2)$$

In this study, the method introduced by Wilke and colleagues (2006; 2007) was used. The method combines the weighted average approach with a bootstrap resampling procedure to further increase the robustness of the *LI*. The data was first thresholded and masked by the ROI, generating left and right data sets. From the left and right data a number (*n*) of bootstrapped re-samples were generated. *LIs* were calculated according to Eq. (1). Then, the *LI* for all possible combinations (*n*<sup>2</sup>) of the re-sampled data sets were calculated, and a trimmed mean of the *n*<sup>2</sup> *LIs* was calculated. This procedure was repeated for 20 thresholds equally spaced between zero and the maximum t-value within the ROI according to the default values (Wilke et al., 2006), and the final *LI* was calculated as a weighted average (Eq. 2) of the trimmed means.

### *Dichotic Listening test*

Dichotic listening was assessed by means of a version of the consonant-vowel *Bergen Dichotic Listening Test* (Hugdahl, 1995). In this task, the subjects were presented with auditory verbal stimuli in both ears simultaneously. The perceived stimuli had to be reported

verbally directly after each presentation, according to directions of the examiner who instructed to attend to either: 1) one of the ears, 2) both ears or 3) one of the ears according to the participant's best perception. The stimuli used in the dichotic speech tests were the consonant-vowel combinations of a stop consonant and the letter 'a': /ba/, /da/, /ga/, /ka/, /pa/ and /ta/. The stimuli were combined in dichotic pairs and used in three different conditions, executed in the following order (for details see Hällgren et al., 1998):

1. The non-forced condition: the subjects were instructed to *recall one stimulus*, namely the syllable they perceived best or most clearly (20 dichotic pairs).
2. The free-report condition: the subjects were encouraged to *recall the syllables heard in both ears* (20 dichotic pairs).
3. The directed-report conditions: the subjects were instructed to *recall syllables perceived by one ear*, when attention was directed to either the right or left ear (20 dichotic pairs with instructed attention to the left ear and 20 pairs with instructed attention to the right ear).

Two parameters were calculated; the number of correct answers and right ear advantage (REA). The REA was scored as a lateralization index, defined by the number of correctly repeated items presented to the right ear minus the number of correctly repeated items to the left ear, divided by the total number of correct answers for both ears (Hugdahl, 2003). This definition holds also for the directed-report condition – the subjects always repeated some of the items presented to the non-focused ear. A positive lateralization index means a right ear advantage and thus a positive value for REA.

The dichotic tests were performed in a sound-isolated chamber. The test was delivered through a CD player, an audiometer and earphones (Telephonics TDH 39). The presentation level was 70 dB SPL (C-weighted equivalent level). Pure tone thresholds were established for the frequencies: 500 Hz, 1000 Hz, 2000 Hz and 4000 Hz, in order to ensure that the subjects did not have asymmetrical hearing losses (an interaural difference of more than 10 dB).

### ***Behavioral tasks***

The administered behavioral language tests were selected to ensure a proper assessment of language performance in subjects with a normal to advanced language ability.

The *Test of Language Competence* (TLC) is suitable for investigating higher language abilities, by investigating applied semantics, syntax and pragmatics. The test is translated into

Swedish and proposed to be suitable for discovering subtle speech and language disorders (*Testbatteri för Bedömning av Subtila Språkstörningar*, TBSS) (Laakso et al., 2000). From this test-battery we utilized a subset of seven tasks to determine subtle speech and language disorders (*Bedömning av Subtila Språkstörningar [Assessment of Subtle Language Deficits]*, BeSS) which do not show ceiling effects when applied to healthy individuals (Laakso et al., 2000). The BeSS-test investigates the following abilities: repetition of long sentences, constructing a correct sentence of three words, inference (text understanding), understanding complex logic-grammatical sentences, understanding dubious sentences, understanding metaphors, and describing presented words. Each subtask of 10 questions could give a maximum of 30 points, maximal total 210 points. Two well-known word retrieval tasks from the TLC were also selected. The *Boston Naming Test* (BNT), consisting of 60 pictures which have to be named, detects naming abilities and correlates with education level (Kaplan et al., 1983; Zec et al., 2007). The Swedish norm established by Tallberg (2005) was used in this study. Furthermore we used a verbal fluency test. The subject was cued with a letter (F, A, S) and had to generate as many words as possible within a minute (FAS-test, Friedman et al., 1998; Loonstra et al., 2001). The Swedish norm, depending on age and gender, is predictive of intellectual level (Tallberg et al., 2008). Lastly, a *Reading task* selected from the Swedish exam for university students was used. The subjects had to read three texts and answer four questions for each test, resulting in a maximum score of 12.

Correlations between the results from fMRI, dichotic listening and language performance tasks were tested with a two-tailed significance test using GraphPad Prism (GraphPad software, Inc. San Diego, USA).  $p < 0.05$  was considered as significant.

## **Results**

### *fMRI results*

When contrasted with the non-language control condition, the sentence completion paradigm elicited clusters of activation in the primary language areas in the left hemisphere, namely in the posterior temporal lobe (corresponding to Wernicke's area) and the left inferior frontal gyrus (corresponding to Broca's area). Also the frontal temporal lobe, the superior parietal lobe and the anterior cingulate cortex were activated. Furthermore, activation was observed in the occipital lobe including the fusiform areas. In Fig. 1, the group activity (orange) that remains after applying an inclusive map of ROIs (blue) as described in Materials and Methods can be seen. The remaining group activation is superimposed over the ROIs. Note that the anterior cingulate ROIs are not depicted.

### *Correlation of dichotic listening with fMRI-LI*

The results of the three dichotic listening conditions (non-forced, free-report, directed-report left/right) were correlated with *LIs* derived from the fMRI paradigm. The results are found in Table 1 and Figure 2.

The non-forced condition REA was significantly positively correlated ( $p < 0.05$ ) with fMRI-*LI* in the anterior cingulate cortex.

In the free-report condition, which demands attention to both ears, the REA correlated positively ( $p < 0.01$ ) with fMRI-*LI* in the superior parietal lobe.

In the directed-report condition, a significant positive correlation ( $p < 0.01$ ) of directed-report-left REA with the fMRI-*LI* in the posterior temporal lobe, which includes Wernicke's area, was found.

Neither the fMRI-*LIs*, nor the dichotic listening REA *LIs* correlated with age.

### *Correlating dichotic listening with language ability*

Performance in all behavioral language tasks except the BNT correlated positively with left-ear reports during the directed left condition of the dichotic listening test (Table 2, Figure III).

Only the FAS test correlated with the amount of right ear reports in the free report condition. Notably, the reading test (LäS) and the BeSS test showed negative correlations with REA during the directed-report-left condition and the free-report condition, respectively.

### *Correlating fMRI-LI with language performance*

fMRI-LI, determined from the posterior temporal lobe including Wernicke's area correlated negatively ( $p < 0.05$ ) with reading ability (LäS),  $r = -0.55$  (Table 3). Performance in the cognitive assessment task, measuring subtle language dysfunctions (BeSS) correlated negatively ( $p < 0.05$ ) with LI in the inferior frontal cortex (Broca's area)  $r = -0.56$  (Figure IV).

## **Discussion**

The purpose of this study was twofold. First, we wished to compare *LI* derived from ROIs acquired with fMRI with estimates of *LI* obtained with Hugdahl's implementation of the classical dichotic listening task (Hugdahl, 1995), in order to evaluate the usability of either method in clinical settings. Second, we were interested in delineating the relation between measures of *LI* and performance on a set of salient language tasks, typically used in the clinical assessment of language impairment. In particular, we sought to clarify whether *LI* varied between subjects performing high or low in the language tasks.

In keeping with the findings in previous investigations (Fernandes, et al., 2006, Fontoura et al., 2008), fMRI and dichotic listening generated similar measures of laterality. However, in contrast to previous reports, the correlation of dichotic-listening- with fMRI-derived *LIs* varied according to the task demands of the different dichotic listening conditions. In the non-forced condition (where subjects are asked to repeat the most noticeable stimuli), a less prominent right ear advantage was associated with more bilateral cingulate cortex activation. The anterior cingulate, as well as the orbitofrontal cortex, is involved in monitoring behaviorally motivated stimuli, a process that may be crucial to performance in the non-forced condition (Luu and Posner, 2003).

In contrast, performance in the condition where subjects were asked to report lateralized stimuli (directed-report-left) correlated with activity in the posterior temporal region, where subjects with less right ear advantage show involvement of the right posterior temporal lobe in addition to the left. This is clearly a finding much in keeping with previous reports of neuroimaging of dichotic listening (*e.g.*, van den Noort, 2008). The activation observed in the right-hemispheric counterpart of Wernicke's area in the temporal lobe strengthens the hypothesis of Grodzinsky and Friederici (2006), who linked this area to lexical and syntactic information integration. Moreover, the temporal lobe is known to be responsible for processing phonological information, not exclusively, but proven to be vital for perception of language (Gernsbacher and Kaschak, 2003). The dichotic listening task is very clearly a task of phonological perception which requires involvement of the left posterior temporal lobe, which we indeed have found. The right-hemispheric activation might indicate additional resources required for the process of integrating phonological input. Finally, the free-report condition, which presumably is more similar to conventional working memory tasks than the other two conditions, rests more upon recruitment of attentional resources. A less pronounced

right ear advantage shows to correlate with more activity in the right-hemispheric superior parietal lobe in addition to left-hemispheric superior parietal lobe activation. Next to hypothesized involvement in reading and word classification/production (Ino et al., 2008; Shapiro et al., 2006), important portions of the parietal cortex are involved in attention mechanisms (Yantis and Serences, 2003, Behrmann et al., 2004).

Both dichotic listening and fMRI have important functions in the assessment of language lateralization. Given the employment of a relevant language task, fMRI can provide a relatively direct account of brain physiology. However, limitations with respect to cost and availability may make fMRI a less likely choice for routine clinical assessment of lateralization. Furthermore, fMRI may be compromised by pathological changes (such as edema or cortical atrophy) or postoperative distortion (*e.g.*, effects of blood material, signal dropout). Under such circumstances, behavioral measures such as dichotic listening may provide more reliable clues to specific aspects of brain function. Although the latter point rarely has been examined in patients with brain damage, it is still important to know how fMRI results and behavioral measures relate to each other. According to our findings, the directed-report-left condition of the *Bergen Dichotic Listening Test* indicated lateralization with respect to the posterior temporal lobe, which is likely to be the cortical region of choice when assessment of language lateralization is warranted (Van den Noort et al., 2008).

Secondly, we aimed to clarify the relation between dichotic listening as well as the fMRI-derived *LI* and clinically salient language tasks. Interestingly, better performance on reporting stimuli presented to the left ear correlated with better language ability. Although the level of significance ( $p < 0.05$ ) was not strong, findings were consistent for all language tasks in the directed-report-left condition. Both BeSS and reading test results were reflected in the REA calculation, for the free-report and the directed-report-left condition respectively.

With respect to fMRI-*LI*, two of our tasks, BeSS and the reading task, provided clear evidence for an association. The reading task exhibited a correlation with *LI* of the posterior temporal cortex, a finding that we believe reflects the well-known connection between reading, reading impairment and temporoparietal structures (Price, 2000; Price et al., 2003, Hillis et al., 2008). In addition, a particularly interesting finding was that the correlation was negative, that is, better performance was related to an attenuated *LI*. This outcome suggests the involvement of right-hemisphere mechanisms in reading. Such mechanisms need not be related to language in the strict sense in that reading also draws upon perceptual and visuospatial skills, which may recruit posterior cortical processes. Furthermore, it is intriguing to see that the fMRI results

lead to the same conclusion as shown by the results of the dichotic listening test; *i.e.* increased right-hemispheric involvement results in increased performance in various language tasks. When discussing these results it is interesting to note that other researchers have recently demonstrated results indicating a variation in brain lateralization during various language tasks. However these researchers have used different techniques (Stroobant et al., 2009) and observed partially dissociated lateralization patterns within the language network, inconsistent with an overall “dominance” model (Pinel and Dehaene, 2009).

Considering the BeSS test (Fig. 4) a similar, but non-significant correlation with the posterior temporal lobe was noted. More conspicuously, BeSS performance was negatively correlated with Broca *LI*. Given the complex nature of the BeSS, the outcome may reflect several functions (perhaps simultaneously) of the anterior language cortices. Broca’s area is involved in subtle grammatical decisions (Damasio, 1992; Ullman et al., 2005, Rodd et al., 2005). Furthermore, Broca’s area may be recruited in working memory tasks; the BeSS battery clearly involves such tasks. Finally, BeSS performance may be facilitated by covert and perhaps even overt vocalizations. Such extra-linguistic behaviors clearly thrive upon anterior language areas (Huang et al., 2001).

Results were considered statistically significant if  $p < 0.05$ . Given the large number of tests performed, a few of the significant results probably reached this level by chance only. This fact inevitably cast some doubt on the conclusions drawn. However, our conclusions are based on collective evidence from several significant correlations. Moreover, all of the significant results were consistent, which led us to believe that the conclusions drawn likely will retain their validity. We tested post-hoc for any correlations between gender and ROI activation using ANOVA with Bonferroni multiple comparison post-tests, however we found no correlation, ensuring the validity of the presented analyses.

Nevertheless, many of our conclusions must remain tentative. Our findings are based upon correlations between different measures, and we employed a relatively limited number of measurements considering the complex nature of the response. In a follow-up study, we aim to investigate the nature of task demands in comparison with language ability. This study will shed light on the difference between fMRI activation and laterality indices brought forth by attention or cognitive demand and activation related to individual language ability. To further

corroborate the main findings, it would be necessary to implement dichotic listening as well as the most promising language tasks (*i.e.* BeSS or possibly the reading task) in the MR-setting, as reported recently by Van den Noort and coworkers (2008) who used a sparse sampling paradigm. Likewise, it would be instructive to study the complexity of the BeSS-subtasks using the MR-scanner.

However, assuming that our conclusions are correct, two inferences can be made about the utility of behavioral measures of *LI*. First, when dichotic listening is used to indicate *LI*, primarily posterior language areas are implicated. Second, in order to assess anterior language *LI*, other tasks should be considered. Our data indicate that BeSS may be of particular interest in this regard.

A stronger implication of our data - which obviously has implications far beyond the utility of selective language tasks or clinical assessment tools - regards the contribution of areas beyond the classical left language areas to language performance. Right-hemispheric counterparts to the language areas of the left hemisphere (Broca's and Wernicke's area) were implicated in that higher performance in some tasks (in particular the BeSS) corresponded to attenuated left-sided *LI* both determined by fMRI and dichotic listening. A straightforward interpretation of this pattern is that subjects better able to report stimuli presented to either ear are also able to recruit and modulate activity in networks distinct from left-hemisphere language areas. Hence, it is important to investigate whether this is the result of 'intrinsic' properties of subjects (*e.g.* pre-experimental verbal skill or intelligence) or the result of the difficulty of the task (such that high performers in the current task would show similar activity as low performers if the task were made more difficult). Furthermore, it would be instructive to know if such putative links between pre-experimental skill and tasks difficulty are specific to language or if they generalize to non-linguistic domains.

We wish to emphasize that our results do not generalize directly to patients with various language problems who might have atypical lateralization due to reorganization of language networks. Neither can direct inferences of the performance-related laterality indices regarding language lateralization in developing children be made. Children, especially those young of age, are in the midst of language development may have a less defined lateralization of language (Vannest et al., 2009). In a recent fMRI study (Schafer et al., 2009) left hemispheric activation was shown to correlate with task accuracy in children, contrasting with the findings for adults in this study. This indicates the importance of studies investigating brain activation

and connectivity related to language ability of healthy adults.

## **Conclusions**

Laterality indices assessed using fMRI in the anterior cingulate cortex, superior parietal lobe, and the posterior temporal lobe, correlated with dichotic listening derived laterality measurements. Compared to dichotic listening, fMRI-LIs are region specific, which is a clear advantage. Results in this study may direct the development of fMRI-derived LIs for clinical assessment of language laterality in specific parts of the brain. However, as fMRI has limitations with respect to cost and availability, behavioral measures such as dichotic listening will remain important.

A particularly interesting finding was that the right-sided posterior temporal cortex, but not the superior parietal lobe, showed increased activation in subjects that performed better in salient clinical language tasks; the same occurred for the right-hemispheric homologue of Broca's area. In concordance, decreased right-ear dominance (and increased reporting of left-ear presented stimuli when focusing attention on the left ear) correlated with a higher performance in all presented language tasks. Thus, more bilateral activation in classical language areas rather than left-hemispheric dominance during language processing indicates higher language ability.

Our presented results, acquired using (1) dichotic listening, (2) fMRI and (3) behavioral language tasks indicated a supporting role of non-classical language areas in the brain in language performance, where mainly right-hemispheric counterparts of Broca's and Wernicke's areas are involved.

## **Acknowledgements**

The contributions of research funding from the Cancer Foundation, University Hospital Research Funds, Ståhl's foundation, the County Council of Östergötland, and the University of Linköping are gratefully acknowledged. In addition, the measurements were performed with use of equipment that to a large extent was funded by the K and A Wallenberg Foundation, to which we would also like to express our gratitude. Finally, we would also like to express our appreciation for the enthusiastic support from our colleagues for our research in

this area. Cecilia Nellie and Jennie Pettersson are especially acknowledged for administrating the behavioral language tasks.

## References

- Abdullaev, Y.G., Posner, M.I., 1997. Time course of activating brain areas in generating verbal associations. *Psychol Sci* 8, 56-59.
- Angrilli, A., Spironelli, C., Elbert, T., Crow, T.J., Marano, G., Stegagno, L., 2009. Schizophrenia as failure of left hemispheric dominance for the phonological component of language. *PLoS ONE* 4, e4507.
- Baxendale, S., 2009- The Wada test. *Curr Opin Neurol* 22, 185-189.
- Beeman, M.J., Chiarello, C., 1998. Complementary right- and left-hemisphere language comprehension. *Curr Dir Psychol Sci* 7, 2-8.
- Behrmann, M., Geng, J.J., Shomstein, S., 2004. Parietal cortex and attention. *Curr Op Neurobiol* 14, 212-217.
- Benjamini, Y., Hochberg, Y., 1995. Controlling the False Discovery Rate: A practical and powerful approach to multiple testing. *J R Stat Soc B* 57, 289-300.
- Bleich-Cohen, M., Hendler, T., Kotler, M., Strous, R.D., 2009. Reduced language lateralization in first-episode schizophrenia: An fMRI index of functional asymmetry. *Psychiatry Res* 171, 82-93.
- Bookheimer, S., 2002. Functional MRI of language: new approaches to understanding the cortical organization of semantic processing. *Annu Rev Neurosci* 25, 151-188.
- Carreiras M., Riba, J., Vergara, M., Heldmann, M., Münte, TF., 2009. Syllable congruency and word frequency effects on brain activation. (Epub ahead of print) *Hum Brain Mapp*, Jan. 26.
- Chiarello, C., 1998. On codes of meaning and the meaning of codes: semantic access and retrieval within and between hemispheres. In M. Beeman & C. Chiarello (Eds.), *Right hemisphere language comprehension: perspectives from cognitive neuroscience*. Erlbaum, Mahwah, pp. 141-160.
- Damasio, A.R., 1992. Aphasia. *New England J Medic* 326, 531-539.
- Damasio, H., Tranel, D., Grabowski, T., Adolphs, R., Damasio, A., 2004. Neural systems behind word and concept retrieval. *Cognition* 92, 179-229.

- Desmond, J.E., Sum, J.M., Wagner, A.D., Demb, J.B., Shear, P.K., Glover, G.H., Gabrieli, J.D., Morrell, M.J., 1995. Functional MRI measurement of language lateralization in Wada-tested patients. *Brain* 118, 1411-1419.
- Dräger, B., Jansen, A., Bruchmann, S., Förster, A.F., Pleger, B., Zwitserlood, P., Knecht, S. 2004. How does the brain accommodate to increased task difficulty in word finding? A functional MRI study. *NeuroImage* 23, 1152-1160.
- Ellis, S.J., Ellis, P.J., Marshall, E., Windridge, C., Jones, S., 1998. Is forced dextrality an explanation for the fall in the prevalence of sinistrality with age? A study in northern England. *J Epidemiol Community Health* 52, 41-44.
- Faust, M., 1998. Obtaining evidence of language comprehension from sentence priming. In M. Beeman & C. Chiarello (Eds.), *Right hemisphere language comprehension: perspectives from cognitive neuroscience*. Erlbaum, Mahwah, pp. 141-160.
- Fernandes, M.A., Smith, M.L., Logan, W., Crawley, A., McAndrews, M.R., 2006. Comparing language lateralization determined by dichotic listening and fMRI activation in frontal and temporal lobes in children with epilepsy. *Brain Lang* 96, 106-114.
- Fletcher, P.C., Happé, F., Frith, U., Baker, S.C., Dolan, R.J., Frackowiak, R.S.J., Frith, C.D. 1995. Other minds in the brain: a functional imaging study of "theory of mind" in story comprehension. *Cognition* 57, 109-128.
- Fontoura, D.R., Branco, D.M., Anés, M., Costa, J.C., Portuguez, M.W., 2008. Language brain dominance in patients with refractory temporal lobe epilepsy. *Arq Neuropsiquiatr* 66, 34-39.
- Friedman, L., Kenny, J.T., Wise, A.L., Wu, D., Stuve, T.A., Miller, D.A., Jesberger, J.A., Lewin, J.S., 1998. Brain activation during silent word generation evaluated with functional MRI. *Brain Lang* 64, 231-256.
- Fu, C.H.Y., Morgan, K., Suckling, J., Williams, S.C.R., Andrew, C., Vythelingum, G.N., McGuire, P.K., 2001. A functional Magnetic Resonance Imaging study of overt letter verbal fluency using a clustered acquisition sequence: Greater anterior cingulate activation with increased task demand. *NeuroImage* 17, 871-879.
- Geffen, G., Traub, E., Stierman, I., 1978. Language assessed by unilateral ECT and dichotic monitoring. *J Neurol Neurosurg Psychiatry* 41, 34-360.
- Gernsbacher, M.A., Kaschak, M.P., 2003. Neuroimaging studies of language production and

- comprehension. *Annu. Rev. Psychol.* 54, 91-114.
- Geschwind, N., 1965, Disconnexion syndromes in animals and man. I. *Brain* 88, 237-294.
- Grodzinsky, Y., Friederici, A.D., 2006. Neuroimaging of syntax and syntactic processing. *Neurobiology* 16, 240-246.
- Hällgren, M., Johansson, M., Larsby, B., Arlinger, S, 1998. Dichotic speech tests. *Scand Audiol Suppl* 49, 35-39.
- Hickok, G., Poeppel, D., 2004. Dorsal and ventral streams: A framework for understanding aspects of the functional anatomy of language. *Cognition* 92, 67-99.
- Hillis, A.E., 2008. Cognitive processes underlying reading and writing and their neural substrates. In G. Goldenberg & B. L. Miller (Eds.) *Handbook of Clinical Neurology*, Vol. 88 (3rd series): Neuropsychology and behavioral neurology. Elsevier, Amsterdam, pp. 311-322.
- Huang, J., Carr, T. H., Cao, Y., 2001. Comparing cortical activations for silent and overt speech using event-related fMRI. *Hum Brain Mapp* 15, 39-53.
- Hugdahl, K., 1995. Dichotic listening: probing temporal lobe functional integrity. In: Davidson, R.J., Hugdahl, K. (Eds.), *Brain asymmetry*. MIT Press, Cambridge, MA, pp. 123-156.
- Hugdahl, K., Carlsson, G., Uvebrant, P., Lundervold, A.J., 1997. Dichotic-listening performance and intracarotid injections of amobarbital in children and adolescents. Preoperative and postoperative comparisons. *Arch Neurol* 54, 1494-1500.
- Hugdahl, K., 2003. Dichotic listening in the study of auditory laterality. In: Hugdahl, K., Davidsson, R.J., (Eds) *The asymmetrical brain*. MIT Press, Cambridge, MA, pp. 441-466.
- Ino, T., Tokumoto, K., Usami, K., Kimura T., Hashimoto, Y., Fukuyama, H., 2008. Longitudinal fMRI study of reading in a patient with letter-by-letter reading. *Cortex* 44, 773-781.
- Just, M.A., Carpenter, P.A., Keller, T.A., Eddy, W.F., Thulborn, K.R., 1996. Brain activation modulated by sentence comprehension. *Science* 274, 114-116.
- Kaplan, E., Goodglass, H., Weintraub, S., 1983. *The Boston Naming Test*. Lea & Febiger, Erlbaum.
- Kimura, D., 1961. Cerebral dominance and the perception of verbal stimuli. *Canad J Psychol*

- 15, 166-171.
- Kircher, T., Brammer, M., Tous Andreu, N., Williams S., McGuire, P., 2001. Engagement of right temporal cortex during processing of linguistic context. *Neuropsychologia* 39: 798-809.
- Koivisto, M., 1997. Time course of semantic activation in the cerebral hemispheres. *Neuropsychologia* 35, 497-504.
- Laakso, K., Brunnegård, K., Hartelius, L., Ahlsén, E., 2000. Assessing high-level language in individuals with multiple sclerosis: A pilot study. *Clin Linguist Phon* 14, 329-349.
- Lee, D., Swanson, S.J., Sabsevitz, D.S., Hammeke, T.A., Winstanley, F.S., Possing, E.T., Binder, J.R., 2008. Functional MRI and Wada studies in patients with interhemispheric dissociation of language functions. *Epilepsy Behav* 13, 350-356.
- Loonstra, A.S., Tarlow, A.R., Sellers, A.H., 2001. COWAT metanorms across age, education, and gender. *Appl Neuropsychol* 8, 161-166.
- Luu, P., Posner, M.I. , 2003. Anterior cingulate cortex regulation of sympathetic activity. *Brain* 126, 2119-2120.
- Lurito, J.T., Kareken, D.A., Lowe, M.J., Chen, S.H.A., Mathews, V.P., 2000. Comparison of rhyming and word generation with fMRI. *Hum Brain Mapp* 10, 99-106.
- Maldjian, J.A., Laurienti, P.J., Burdette, J.H., Kraft, R.A., 2003. An automated method for neuroanatomic and cytoarchitectonic atlas-based interrogation of fMRI data sets. *NeuroImage* 19, 1233-1239.
- McDonald, S.A., Tamariz, M., 2002. Completion norms for 112 Spanish sentences. *Behav Res Methods Instrum Comput* 34, 128-137.
- Pernet, C., Andersson, J., Paulesu, E., Demonet, J.F., 2009. When all hypotheses are right: A multifocal account of dyslexia. (Epub ahead of print) *Hum Brain Mapp*, Feb. 23.
- Pinel, P., Dehaene, S., 2009. Beyond hemispheric dominance: Brain regions underlying the joint lateralization of language and arithmetic to the left hemisphere. (Epub ahead of print) *J Cogn Neurosci*, Jan 13.
- Price, C.J., 2000. The anatomy of language: contributions from functional neuroimaging. *J Anat* 197, 335-359.
- Price, C.J., Gorno-Tempini, M.L., Graham, K.S., Biggio, N., Mechelli, A., Patterson, K.,

- Noppeney, U., 2003. Normal and pathological reading: converging data from lesion and imaging studies. *NeuroImage* 20, 30-41.
- Rodd, J. M., Davis, M. H., Johnsrude, I. H., 2005. The neural mechanisms of speech comprehension: fMRI studies of semantic ambiguity. *Cer Cor* 15, 1261–1269.
- Schafer, R.J., Lacadie, C., Vohr, B., Kesler, S.R., Katz, K.H., Schneider, K.C., Pugh, K.R., Makuch, R.W., Reiss, A.L., Constable, R.T., Ment, L.R., 2009. Alterations in functional connectivity.
- Shapiro, K.A., Moo, L.R., Caramazza, A., 2006. Cortical signatures of noun and verb production. *Proc Natl Acad Sci U S A* 103, 1644-1649.
- Spreer, J., Arnold, S., Quiske, A., Wohlfarth, R., Ziyeh, S., Altenmüller, D., Herpers, M., Kassubek, J., Klisch, J., Steinhoff, B.J., Honegger, J., Schulze-Bonhage, A., Schumacher, M., 2002. Determination of hemisphere dominance for language: comparison of frontal and temporal fMRI activation with intracarotid amyntal testing. *Neuroradiology* 44, 467-474.
- Strauss E., Gaddes W.H., Wada, J., 1987. Performance on a free-recall verbal dichotic listening task and cerebral dominance determined by the carotid amyntal test. *Neuropsychologia* 25, 747-753.
- Stroobant, N., Buijs, D., Vingerhoets, G., 2009. Variation in brain lateralization during various language tasks: A functional transcranial Doppler study. *Behav Brain Res* 199, 190-196.
- Szaflarski, J.P., Binder, J.R., Possing, E.T., McKiernan, K.A., Ward, B.D., Hammeke, T.A., 2002. Language lateralization in left-handed and ambidextrous people: fMRI data. *Neurology* 59, 238-244.
- Tallberg, I.M., 2005. The Boston Naming Test in Swedish: Normative data. *Brain Lang* 94, 19-31.
- Tallberg, I.M., Ivachova, E., Jones Tinghag K., Östberg, P., 2008. Swedish norms for word fluency tests: FAS, animals and verbs. *Scand J Psych* 49, 479-485.
- Ullman, M.T., Pancheva, R., Love, T., Yee, E., Swinney, D., Hickok, G., 2005. Neural correlates of lexicon and grammar: Evidence from the production, reading and judgment of inflection in aphasia. *Brain Lang* 93, 185-238.

- van den Noort, M., Specht, K., Rimol, L.M., Ersland, L., Hugdahl, K., 2008. A new verbal reports fMRI dichotic listening paradigm for studies of hemispheric asymmetry. *NeuroImage* 40, 902-911.
- Vannest, J., Karunanayaka, P.R., Schmithorst, V.J., Szaflarski, J.P., Holland, S.K., 2009. Language networks in children: evidence from functional MRI studies. *AJR* 192, 1190-1196.
- Wilke, M., Schmithorst, V.J., 2006. A combined bootstrap/histogram analysis approach for computing a lateralization index from neuroimaging data. *NeuroImage* 22, 522-530.
- Wilke, M., Lidzba, K., 2007. LI-tool: A new toolbox to assess lateralization in functional MR-data'. *J Neurosci Methods* 163, 128-136.
- Wise, J.S.R., Scott, S.K., Blank, S.C., Mummery, C.J., Murphy, K., Warburton, E.A., 2001. Separate neural subsystems within 'Wernicke's area'. *Brain* 124, 83-95.
- Yantis, S., Serences, J.T., 2003. Cortical mechanisms of space-based and object-based attentional control. *Curr Opin Neurobiol* 13, 187-193.
- Yetkin, F.Z., Hammeke, T.A., Swanson, S.J., Morris, G.L., Mueller, W.M., McAuliffe, T.L., Haughton, V.M., 1995. A comparison of functional MR activation patterns during silent and audible language tasks. *Am J Neuroradiol* 16, 1087-1092.
- Zec, R.F., Burkett, N.R., Markwell, S.J., Larsen, D.L., 2007. Normative data stratified for age, education, and gender on the Boston Naming Test. *Clin Neuropsychol* 21, 617-637.

**Table 1.** Significant correlations (Pearson's  $r$ ) between dichotic listening REA and fMRI LI in the regions of interest. \* =  $p < 0.05$ , \*\* =  $p < 0.01$ .

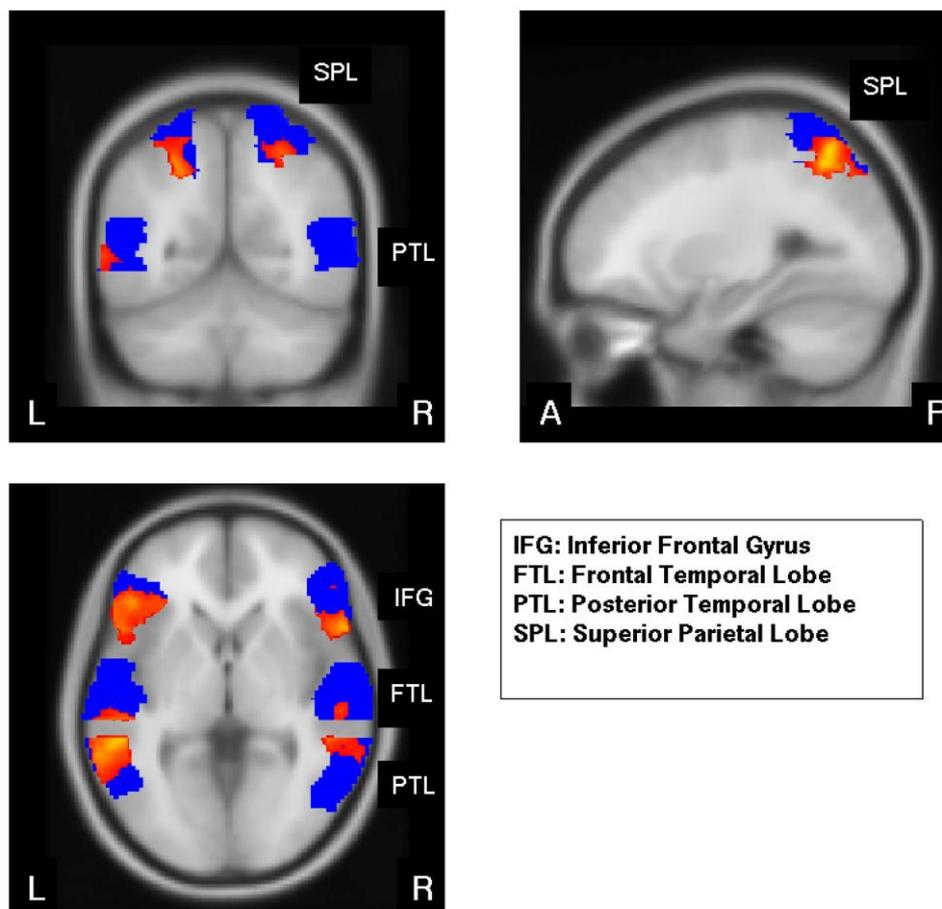
	Anterior Temporal Lobe	Posterior Temporal Lobe	Inferior Frontal Gyrus / Broca's area	Superior Parietal Lobe	Anterior Cingulate Cortex
Non-forced	-	-	-	-	0.56*
Free-report	-	-	-	0.68**	-
Directed- report left	-	0.65**	-	-	-
Directed- report right	-	-	-	-	-

**Table 2.** Significant correlations (Pearson's  $r$ ) between dichotic listening and behavioural language tests. \* =  $p < 0.05$ , \*\* =  $p < 0.01$ . FAS = fluency test, Läs = reading test, BeSS = cognitive ability.

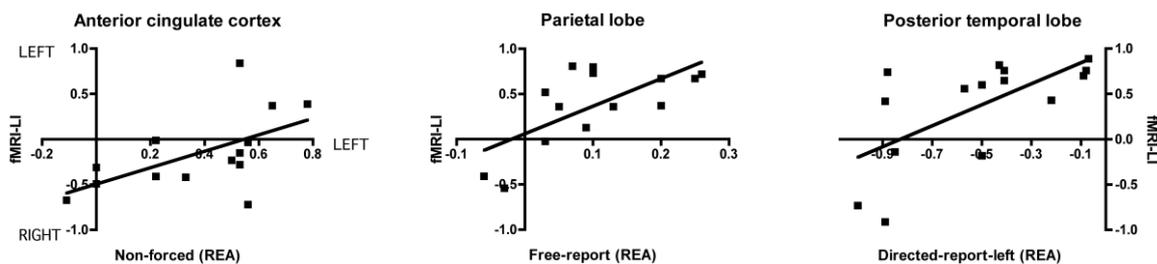
	FAS	Läs	BeSS
Non-forced (REA)	-	-	-
Free-report (REA)	-	-	-0.53*
Directed-report-left (REA)	-	-0.56*	-
Directed-report-right (REA)	-	-	-
Non-forced, left ear	-	-	-
Non-forced, right ear	-	-	-
Free-report, left ear	-	-	0.58*
Free-report, right ear	0.52*	-	-
Directed-report-left, left ear	0.52*	0.69**	0.62*
Directed-report-left, right ear	-	-	-
Directed-report-right, left ear	-	-	-
Directed-report-right, right ear	-	-	-

**Table 3.** Significant correlations (Pearson's r) between language performance tests and fMRI LI in regions of interest. \* =  $p < 0.05$ , ns = non significant ( $p = 0.07$ ), FAS = fluency test, Läs = reading test, BeSS = cognitive ability, BNT = Boston Naming Test.

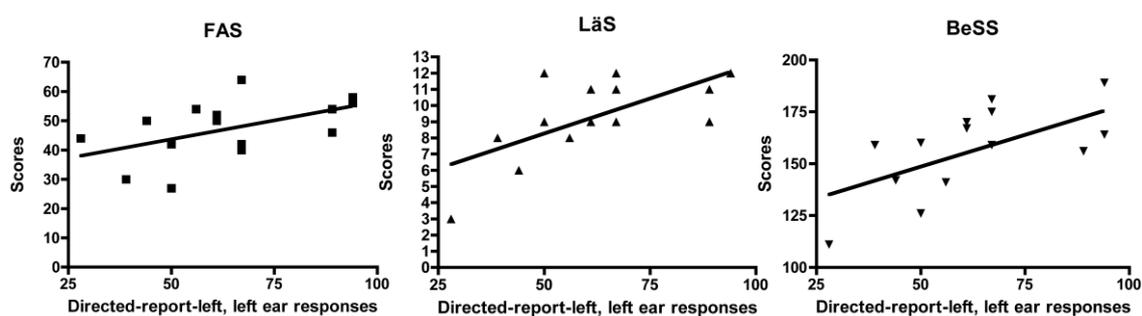
	Anterior Temporal Lobe	Posterior Temporal Lobe	Inferior Frontal Gyrus / Broca's Area	Superior Parietal Lobe	Anterior Cingulate Cortex
FAS	-	-	-	-	-
Läs	-	-0.55*	-	-	-
BeSS	-	-0.48 <sup>ns</sup>	-0.56*	-	-
BNT	-	-	-	-	-



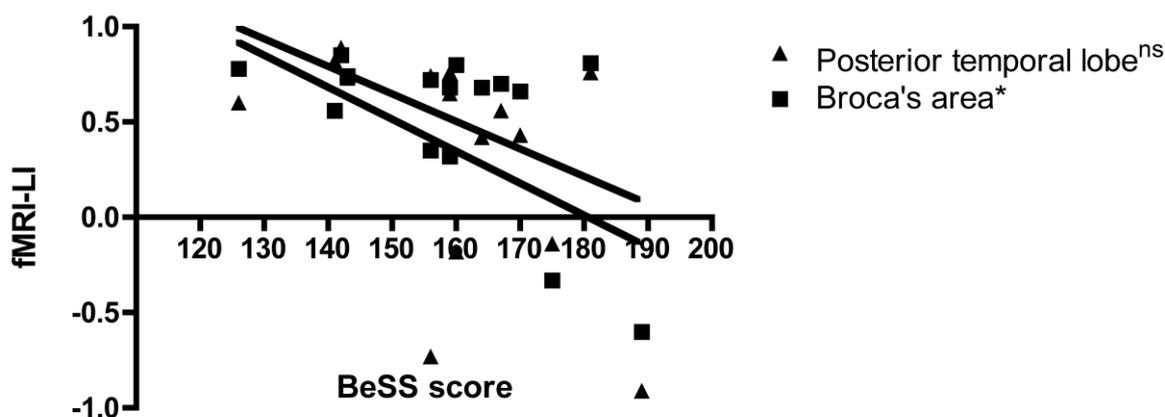
**Figure 1.** MR image showing the functional ROIs (blue) used for LI calculations and ROI specific group activations (orange). This group analysis was restricted to the ROIs and thresholded at  $p = 0.05$  (FDR).



**Figure 2.** Correlation between dichotic listening non-forced, free-report and directed-report-left conditions and fMRI-LI. Left and right on the axes indicate the hemispheres.



**Figure 3.** Correlation between correct left ear answers at the dichotic listening directed-report-left condition and performance on the behavioral language tests (higher score means higher performance): FAS = fluency test, Läs = reading test, BeSS = language ability



**Figure 4.** Correlation between LI assessed by fMRI and the Battery for Subtle Language impairment Score (BeSS).