Low-frequency fluctuations (LFFs) are a major source of variation in fMRI data. This has been established in numerous experiments—particularly in the resting state. Here we investigate LFFs in a task-dependent setting. We hypothesized that LFFs may contain information about cognitive networks that are specific to the overall task domain without being time locked to stimulus onsets. We analyzed data of 6 fMRI experiments, 4 of which belonged to the language domain. After regressing out specifics of the experimental design and low-pass filtering (<0.1 Hz), we found that the 4 language experiments produced a correlational pattern that was not present in the 2 nonlanguage studies. Specifically, a region in the posterior part of the left superior temporal sulcus/gyrus was consistently correlated with both the left Brodmann’s area 44 and the left frontal operculum in all 4 language studies, whereas this correlation was not found in the 2 other experiments. This finding indicates the existence of a basic network that acts as a general framework for language processing. In contrast to networks obtained by a conventional conjunction analysis of activation maps, this network is independent of experimental specifics such as stimulus onsets and exists in the low-frequency range.

Keywords: conjunction analysis, fMRI, language studies, low-frequency fluctuations, superior temporal sulcus

Introduction

In recent years, a set of brain regions such as Broca’s area or parts of the superior temporal sulcus/gyrus (STS/STG) and many others were found to be activated in a large range of fMRI studies involving language tasks. However, some of these areas have also been found to be activated in nonlanguage tasks. We therefore hypothesized that the specificity of the activation patterns observed in fMRI studies on language might not lie in the individual areas themselves but rather in the constitution of the overall network. The aim of the present study was to identify such language-specific networks by analyzing low-frequency fluctuations (LFFs) of fMRI signals.

It is well known that much of the variation in fMRI time signals is caused by LFFs with < 0.1 Hz whose amplitudes represent a large portion of the overall signal variance of the blood oxygen level-dependent (BOLD) response both at 3T and at 7T (Bianciardi et al. 2009). By restricting our analysis to the low-frequency components of the regression residuals, we can exclude the possibility that any pattern that we might find could be due to details that are time locked to stimulus onsets. Rather, it would indicate the existence of a very basic network that acts as a general framework for language processing, put into operation by the brain when given the context of a language task.

LFFs have been observed in fMRI time series (Biswal et al. 1995) as well as in optical imaging data (Elwell et al. 1994; Mayhew et al. 1996; Obrig et al. 2000; Schroeter et al. 2004). Wise et al. (2004) found that a significant source of LFFs is due to arterial carbon dioxide levels as measured by fMRI in the resting state. Mayhew et al. (1996) found that low-frequency oscillations (<0.1 Hz) observed by imaging scattered and reflected light of the cerebral surface represent a major source of variability in the signal. They attributed this effect to low-frequency vasomotion and peripheral microcirculation unrelated to neuronal events. In addition, respiration has been found to be an important factor in producing LFFs (Birn et al. [2006]). Therefore, such signal components are often looked upon as noise that should be identified and removed because they mask out the event-related signal of interest (Kiviniemi et al. 2003).

However, the origin of LFFs may perhaps not be only vascular in nature but may directly represent neuronal signaling. Evidence for this comes from Fukunaga et al. (2008) who found that low-frequency signal components are of metabolic origin and therefore most likely due to neuronal activity. Furthermore, in a recent simulation study, Honey et al. (2007) showed that LFFs emerge naturally from high-frequency neural interactions suggesting a possible mechanism that produces this phenomenon.

Other studies have analyzed LFFs in resting state fMRI data (Biswal et al. 1995; Goerke et al. 2005), attributing them to spontaneous neuronal activity. In particular, the so-called default mode hypothesis (Raichle et al. 2001; Greicius et al. 2003; Fransson 2006) has a focus on LFFs in the resting brain. Also in the resting brain, Achard et al. (2006) have described a low-frequency functional network spanning many cortical areas that they hypothesize may be a substrate for distributed information processing. Damoiseaux et al. (2006) have found several resting state low-frequency networks to be consistent across subjects.

On the other hand, it has been hypothesized that LFFs in fMRI time series (<0.1 Hz) may reflect not only spontaneous neuronal activity but may also be related to specific tasks or functional domains. In support of this assumption, Leopold et al. (2003) have described low-frequency recordings in the monkey cortex from multiple electrodes that show strong coherence both in a resting state condition and during a visual stimulation. In humans, Stanberry et al. (2006) have found differences in functional connectivity between good readers and dyslexics based on LFFs. Furthermore, Lowe et al. (2000) observed cross-correlations in the low-frequency range (<0.08 Hz) during a spatial working memory task.

In the present paper, we investigate whether cross-correlations in low-frequency fMRI signals can be used to detect domain-specific correlational patterns in language processing.
Materials and Methods

For the present study, data from 6 different fMRI experiments were used. Four of these involved language-related tasks. The other 2 experiments served as controls.

All studies were conducted at the Max Planck Institute for Human Cognitive and Brain Sciences, Leipzig, Germany, between 2003 and 2007. In all 6 experiments, the subjects received an MRI scan acquired on a 3-T magnetic resonance scanner (Siemens Trio, Erlangen, Germany for Experiments 1,2,3 and Bruker, Ettlingen, Germany for Experiments 4,5,6) using an echo planar imaging (EPI) sequence. All subjects gave informed consent. The experiments 1, 2, 3, and 4 involved a language task, and experiments 5 and 6 were nonlanguage tasks that served as control experiments. A more detailed description is given in the following.

Experiments 1 and 2

The first 2 experiments were originally performed for an fMRI study described in Friederici et al. (2006) and were reevaluated here. Sixteen subjects participated in experiments 1 and 17 participated in experiment 2. In both experiments, subjects were visually presented with sequences of consonant-vowel syllables. They were instructed to recognize the grammatical structure of these sequences. The experiments differed with respect to the type of artificial grammar used. In experiment 1, the sequences followed a finite state grammar. In experiment 2, a phrase structure grammar was used.

Functional magnetic resonance images were acquired in a slab of 20 slices covering a central portion of the brain. A gradient-echo EPI sequence was used with time echo (TE) 30 ms, flip angle 90°, and time repetition (TR) = 2 s. The matrix acquired was $128 \times 128$ with a field of view (FOV) of 25.6 cm, resulting in an in-plane resolution of $2 \times 2$ mm. The slice thickness was 3 mm with an interslice gap of 0.6 mm. For more detail on the experimental design and the data acquisition protocol, see Friederici et al. (2006).

Experiments 3

The third experiment was part of a developmental study on syntactic and semantic processing that investigated children and adults. The current analysis included only the data from the adult group. The experiment comprised 3 conditions, correct sentences, semantically incorrect sentences, and syntactically incorrect sentences. These sentences were presented auditorily in a random fashion. Subjects were asked to judge the sentences’ grammaticality. Data from the adults in all 3 conditions entered the analysis. Functional magnetic resonance images were acquired in a slab of 20 slices covering a central portion of the brain. A gradient-echo EPI sequence was used with TE 30 ms, flip angle 90°, and TR = 2 s. The matrix acquired was $64 \times 64$ with an FOV of 19.2 cm, resulting in an in-plane resolution of $3 \times 3$ mm. The slice thickness was 4 mm with an interslice gap of 1 mm. For more detail on the experimental design and the data acquisition protocol, see Brauer and Friederici (2007).

Experiment 4

Experiment 4 was conducted as a study investigating neural correlates of the syntax-semantics interface in language comprehension. Sentences with sequences of consonant-vowel syllables. They were instructed to identify the direction of the arrows while performing a go–nogo task. Functional magnetic resonance images were acquired in a slab of 14 slices covering a central portion of the brain. A gradient-echo EPI sequence was used with TE 30 ms, flip angle 90°, and TR = 2 s. The matrix acquired was $64 \times 64$ with an FOV of 19.2 cm, resulting in an in-plane resolution of $3 \times 3$ mm. The slice thickness was 5 mm with an interslice gap of 1 mm. For more detail on the experimental design and the data acquisition protocol, see Danielmeier et al. (2004).

Data Analysis

The analysis was done using the software package lipsia (Lohmann et al. 2001) using the following processing steps. All data sets were initially aligned with the Talairach coordinate system while being resampled to a spatial resolution of $3 \times 3 \times 3$ mm. Following a preprocessing for motion and removal of baseline drifts $< 0.01$ Hz, the data were further analyzed for correlations in the low-frequency domain between 0.1 and 0.01 Hz.

In order to exclude effects due to stimulus onsets, we concentrated on the information contained in the residuals $e$ of the general linear model (Friston et al. 1995) of the form $K'X_K$ + $e$, where $Y$ denotes the measured time course in one voxel, $X$ represents the design matrix that encoded the experimental stimulation convolved with a hemodynamic model based on the Gamma function, $K$ is a Gaussian smoothing matrix with fwhm $= 4$ s, and $e$ is the residual error. As in Vincent et al. (2006), Friederici et al. (2006) we included a global covariate into the design matrix. This global covariate was obtained by computing the mean signal value across all brain voxels per time step. We discuss the effect of the global covariate in more detail in a later section.

We applied a low-pass filter to the residuals so that the subsequent analysis steps were restricted to LFFs with frequencies below 0.1 Hz. In a separate analysis, we also applied a low-pass filter with a cutoff frequency of 0.04 Hz in order to better determine the frequency range that causes the effects.

We manually defined 2 seed points within Brodmann’s area 44 (BA44 as part of Broca’s area) and a point inside the frontal operculum (FOP) at Talairach coordinates $(+6, 16, 8$ and $-36, 20, 2$, respectively (see figure 1). These 2 regions were chosen because they are prototypical in language tasks and are frequently reported to be engaged in syntax processing (Stormswold et al. 1996; Moro et al. 2001; Roder et al. 2002; Ben-Shachar et al. 2003; Musso et al. 2003; Friederici et al. 2006; Bahlmann et al. 2007; Makuuchi et al. 2009). Here, we used the coordinates reported by Friederici et al. (2006) that were derived from the main effect of grammaticality. We defined 2 regions of interest as spheres around the 2 center points described above (a volume of 33 voxels $\times 401$ mm$^3$ each).

For each of these 2 seed regions, we averaged the preprocessed fMRI time series across all voxels and computed Pearson’s correlation coefficient of the averaged time course with all other voxels in each data set. Nonbrain voxels were excluded via thresholding. We normalized these correlations using Fisher’s r-to-z transform $z = 0.5 \log((1 + r)/(1 - r))$ to enforce Gaussianity of the correlation data and permit subsequent statistical tests.

Experiment 6

This study investigated the influence of action preparation on visual identification of simple visual stimuli (black arrow heads presented against a background of randomly arranged small black lines). Sixteen subjects had to identify the direction of the arrows while performing a go–nogo task.

Functional magnetic resonance images were acquired in a slab of 32 slices covering a central portion of the brain. A gradient-echo EPI sequence was used with TE 30 ms, flip angle 90°, and TR = 2 s. The matrix acquired was $64 \times 64$ with an FOV of 19.2 cm, resulting in an in-plane resolution of $3 \times 3$ mm. The slice thickness was 2.5 mm with an interslice gap of 1 mm. For more detail on the experimental design and the data acquisition protocol, see Hoehl S, Striano T, Friederici AD, Hennenlotter A (unpublished data).
For each of the 6 experiments and the 2 seed regions included in the present study, we performed a voxelwise t-test across subjects yielding a total of 12 correlation maps. We hypothesized that the 4 language-related studies would show a language-specific correlational pattern. The remaining 2 were expected to show a clearly different pattern.

The degree of correspondence across the 4 language experiments was assessed using a conjunction analysis according to the minimum statistic approach described by Nichols et al. (2004). In addition, we also analyzed the correlation maps of all 6 experiments separately. All maps—including the conjunction maps—were corrected for multiple comparisons using the false discovery rate (FDR) method (Benjamini and Hochberg 1995; Genovese et al. 2002) with \( P < 0.05 \). Voxels inside the seed masks were excluded during FDR correction.

**Results**

In a first step, we applied the above processing chain to the data that were low-pass filtered with a cutoff frequency of 0.1 Hz. The results of the conjunction analysis are listed below in Table 1. Significant correlations were found between the seed regions and their contralateral counterparts. In addition, we also found significant correlations between the seed regions and thalamus, nucleus caudatus, and most prominently the left STS (Table 1 and Fig. 2). This latter correlation was more pronounced for the BA44 seed region than for the FOP seed region. Two of the 4 language experiments provided complete brain coverage by the fMRI data. These 2 studies showed an additional set of brain regions correlated with the seeds (Table 2 and Fig. 3). Because correlations with the median wall and the intraparietal sulcus were present not only in the language experiments but also in the nonlanguage experiments, these areas cannot be assumed to be language-specific.

In order to assess whether the areas described above are specific for language experiments, we compared them with results found in 2 nonlanguage experiments. In both cases, we found that the most prominent difference was the presence of correlations between the inferior frontal seed regions and the posterior portion of the left STS. This correlation—clearly present in all language experiments—was not significantly present in the 2 nonlanguage studies (see Table 3 and Figs 4 and 5). In a second test, we repeated the above processing steps using low-pass filtering with a cutoff frequency of 0.04 Hz. We found very similar results (see Supplementary Material).

**Sources of Variance**

In the following, we evaluate possible factors causing the correlations reported in the previous sections. For ease of presentation, we focus on experiment 3 and report results averaged across the subjects that participated in this particular study. We begin by analyzing the percentage of variance explained by the experimental design using the coefficient of
determination defined as $r^2 = \frac{rSS}{tSS}$ where $rSS$ is the regression sum of squares and $tSS$ the total sum of squares. Pearson’s correlation $r$ is obtained by taking the square root of $r^2$. We found that the percentage of variance explained by the hemodynamic model that represented the stimulus onsets was less than 0.15 everywhere in the brain. We then included a global covariate that is obtained by taking the mean across all brain voxels. We found that $r^2$ more than doubled across many brain areas when using the model that was augmented by the global covariate (Fig. 6). This agrees well with previous findings which showed that most of the BOLD signal is related to physiological fluctuations including neuronal activity (Biswal et al. 1996). The residuals on which our correlation results of the previous sections are based were obtained using the augmented model. We recomputed our main result shown in Figure 4 without inclusion of the global covariate and found that the results did not change in a substantial way (see Supplementary Material).

Table 3
Difference between FDR-corrected conjunction map and FDR-corrected correlation map of the nonlanguage experiments 5 (top) and 6 (bottom) with the seed region in BA44

<table>
<thead>
<tr>
<th>Volume</th>
<th>Talairach coordinates</th>
</tr>
</thead>
<tbody>
<tr>
<td>1890</td>
<td>$-53, -47, -3$</td>
</tr>
<tr>
<td>351</td>
<td>$46, 25, 24$</td>
</tr>
<tr>
<td>108</td>
<td>$-41, 16, 24$</td>
</tr>
<tr>
<td>432</td>
<td>$10, 4, 12$</td>
</tr>
<tr>
<td>91</td>
<td>$-11, -8, 18$</td>
</tr>
<tr>
<td>2322</td>
<td>$-53, -29, 6$</td>
</tr>
<tr>
<td>3051</td>
<td>$43, 28, 21$</td>
</tr>
<tr>
<td>432</td>
<td>$10, 4, 12$</td>
</tr>
<tr>
<td>432</td>
<td>$-11, -8, 18$</td>
</tr>
</tbody>
</table>

Note: Only regions where the conjunction of the language studies was significant but the correlation map of experiment 5 or 6 was not significant are listed. In other words, the regions listed above are those that are specific to language as opposed to the nonlanguage studies. Note that there is a marked difference in the left STS between the language studies and the experiments 5 and 6.

Next we checked whether stimulus onsets can be definitely ruled out as a cause of the correlations we found between residuals. Note that although nonlinear correlations might still be present, linear correlations between the experimental design and the unfiltered residuals must be absent because linear dependencies are explicitly factored out in residuals. And indeed, when checking Pearson’s correlation between the unfiltered residuals and the experimental design we found only very small correlations ($r < 0.03$) that may be due to numerical inaccuracies. Low-pass filtering the residuals at a cutoff of 0.1 Hz introduced some slightly larger linear correlations between the filtered residuals and the experimental design but remained below 0.07 everywhere in the brain. Correlations to the seed regions were several times larger—especially in the posterior portion of the STS/STG (Fig. 7). Therefore, specifics of the
The experimental design can indeed be ruled out as a significant factor for the effects shown in Figures 2–5.

Discussion

We found correlational structures between low-pass-filtered residuals in language and nonlanguage task domains that are not related to stimulus onsets but are specific to the overall task domain. In contrast to networks obtained by a conventional conjunction analysis of activation maps, these structures are independent of experimental specifics such as stimulus onsets and exist in the low-frequency range. Because LFFs account for a large portion of the overall variation in fMRI data, this may open a new and interesting road to network detection.

The source of variance that produces these effects is still unclear. Even though the experimental design and the global covariate make up more than half of the total variation in some brain areas, a significant portion of the fMRI signal is still unaccounted for. The observed effects must be caused by signal components contained within this as yet poorly understood part.

In particular, we found significant correlations between seed regions in BA44/FOP and a network of other regions in low-frequency fMRI data. Some parts of the correlational networks appear to be specific to the language domain, whereas others seem to be unspecific. There was one region within the correlational network that appeared to be highly specific to the language domain—namely the posterior portion of the left STS. This region was consistently present in all 4 language experiments but was absent in the 2 controls.

The regions BA44/FOP and the STS/STG in the left hemisphere have consistently been described as parts of a language-related network (Friederici 2002; Hickok and Poeppel 2007). Although activations in BA44 have been shown to specifically increase as a function of processing structural and thematic hierarchies and linear order (Bornkessel et al. 2005; Friederici et al. 2006; Grewe et al. 2006; Brauer and Friederici 2007) and FOP as a function of local phrase structure violation (Friederici et al. 2003, 2006), the left posterior STS/STG has been discussed to support the processing of syntactic, verb argument, and prosodic information (Friederici et al. 2003; Bornkessel et al. 2005; Humphries et al. 2005; Brauer and Friederici 2007); for a review, see Vigneau et al. (2006). These latter findings have lead to the interpretation of the left posterior STS/STG as a region supporting the integration of different information types during perception (Friederici 2002; Grewe et al. 2007) or as an auditory–motor interface (Hickok and Poeppel 2007). Our results agree well with earlier findings by Hampson et al. (2002) who also found correlations in the low-frequency range between Broca’s area and Wernicke’s area in a listening task. They used a steady state experimental design with trial lengths of 45 s or more to create the long durations necessary for investigating the low-frequency range, whereas here we followed a different strategy by analyzing residuals across the entire length of the experiment.

Interestingly, the analysis of the low-frequency correlations indicates a higher correlation of the STS with BA44 than with FOP. This finding can be connected to data from a structural connectivity analysis by means of diffusion tensor imaging with seeds in BA44 and in the left FOP that reveal a connection between BA44 and the posterior STS/STG but a different pathway connecting FOP and the anterior STS/STG. Functionally, the anterior STS/STG has been segregated from the posterior...
STS/STG as the anterior STS/STG has been described to support basic online syntactic processes (Humphries et al. 2001; Dronkers et al. 2004), such as local phrase structure building (Friederici 2002; Friederici et al. 2003), whereas the posterior STS/STG has been interpreted to support integration processes.

A weakness of the present study is that our data were acquired on 2 different scanners and with different imaging parameters so that an unwanted source of variance was introduced. However, the 2 scanners were used in both language and nonlanguage experiments with varying parameters so that effects due to acquisition parameters are unlikely to have caused our results. Nonetheless, further studies should be conducted for validation purposes.

In summary, the present analysis of the LFFs indicates a temporofrontal language-specific network that is independent of the specific functionally varying conditions. The low-frequency data from the different language experiments compared with the nonlanguage experiments suggest that, once the brain is involved in a particular processing domain due to a given input (language) and task (evaluation of language input), it activates the basic language-related network onto which experiment-specific variations only add a minor part.

**Supplementary Material**

Supplementary material can be found at: http://www.cercor.oxfordjournals.org/

**Notes**

Conflict of Interest: None declared.

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