When Broca Goes Uninformed: Reduced Information Flow to Broca’s Area in Schizophrenia Patients With Auditory Hallucinations

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Auditory-verbal hallucinations (AVHs) are frequently associated with activation of the left superior temporal gyrus (including Wernicke’s area), left inferior frontal gyrus (including Broca’s area), and the right hemisphere homologs of both areas. It has been hypothesized that disconnectivity of both interhemispheric transfer and frontal and temporal areas may underlie hallucinations in schizophrenia. We investigated reduced information flow in this circuit for the first time using dynamic causal modeling, which allows for directional inference.

A group of healthy subjects and 2 groups of schizophrenia patients—with and without AVH—performed a task requiring inner speech processing during functional brain scanning. We employed connectivity models between left hemispheric speech-processing areas and their right hemispheric homologs. Bayesian model averaging was used to estimate the connectivity strengths and evaluate group differences. Patients with AVH showed significantly reduced connectivity from Wernicke’s to Broca’s area (97% certainty) and a trend toward a reduction in connectivity from homologs of Broca’s and Wernicke’s areas to Broca’s area (93% and 94% certainty). The connectivity magnitude in patients without hallucinations was found to be intermediate. Our results point toward a reduced input from temporal to frontal language areas in schizophrenia patients with AVH, suggesting that Broca’s activity may be less constrained by perceptual information received from the temporal cortex. In addition, a lack of synchronization between Broca and its homolog may lead to the erroneous interpretation of emotional speech activity from the right hemisphere as coming from an external source.

Key words: auditory-verbal hallucinations/dynamic causal modeling/language network/inner speech/functional brain connectivity

Introduction

Disturbing auditory-verbal hallucinations (AVHs) or “hearing voices” are a characteristic symptom of schizophrenia. Hallucinations have been defined as perceptual experiences in the absence of corresponding external stimuli.1 AVHs are the most prevalent type of hallucinations in schizophrenia.2 They frequently interfere with everyday functioning and reduce the quality of life.3 Research into brain anatomy and function related to AVHs has been accumulating in recent years. Although some key brain regions have been identified, the specific underlying dysfunctions within these regions or abnormalities of interaction between these regions remain to be elucidated.4

Neuroimaging studies of AVH have consistently revealed activation of the left superior temporal gyrus (STG, including the temporoparietal junction [TPJ] or Wernicke’s area) during hallucinations.5 Numerous studies have also demonstrated activation of the left inferior frontal gyrus (IFG, including Broca’s area)5,6 and its homolog, as well as the right temporal cortex (including Wernicke’s homolog).7 Broca’s region, situated in the IFG and Brodmann areas 44/45, is involved in explicit speech production and has also been shown to be activated during speech imagery, or covert speech production.9 Wernicke’s area, which is situated in the posterior section of the STG at the junction with the occipital and parietal...
lobes, including the posterior part of Brodmann area 22 and parts of Brodmann areas 39/40, is involved in the comprehension of language. The right hemisphere homologs of Wernicke’s and Broca’s areas are involved in the emotional context of speech and are strongly connected with their left counterparts.

Rather than dysfunction in a singular brain region, aberrant connectivity within this frontotemporal bihemispheric network may underlie AVH in schizophrenia. However, the few studies that have so far investigated connectivity between the 2 areas in relation to AVH were limited by small sample sizes, lack of a nonhallucinating comparison group, or lack of a task targeting language processing and merely investigated correlations rather than effective connectivity. In addition, Mechelli and colleagues employed dynamic causal modeling (DCM) to investigate the speech evaluation network in patients with AVH. They assumed that poor integration within this network is associated with misidentification of the patient’s own speech as that of somebody else. Indeed, it was found that bottom-up communication between the STG and the anterior cingulate cortex (ACC) was significantly larger for self-generated speech compared to alien speech.

It has been hypothesized that a disconnection of the frontal and temporal areas may underlie hallucinations in schizophrenia. Here, we test this hypothesis using DCM because it allows for a comparison between groups of the strengths of intrinsic connectivity between neuronal populations. DCM is a specialized method for testing a specific hypothesis; thus, it is a convenient technique to validate the hypothesis of disrupted connections between Broca’s area and Wernicke’s area. Of specific interest is also the role of the right IFG (Broca’s homolog), which was shown to be overactive in the largest functional magnetic resonance imaging (fMRI) study of hallucinations to date. A lack of synchronization between both areas may lead to the erroneous interpretation of emotional speech activity from the right hemisphere as coming from an external source.

**Methods**

**Subjects**

Data from 47 schizophrenia patients and 31 healthy subjects were included, after written informed consent was obtained. Subjects participated in 1 of 2 studies at our Neuroimaging Center over the past 5 years, in which the metrical stress evaluation task was used. The diagnosis of schizophrenia was confirmed by the Schedules for Clinical Assessment in Neuropsychiatry (SCAN 2.1) interview. The severity of symptoms was determined by the Positive and Negative Syndrome Scale (PANSS) interview. Patients were divided into 2 groups according to the hallucination item (P3) of the PANSS: a group with AVH (AVH group, n = 30)—scoring above 3 (a score corresponding to “mild” psychopathology); and without AVH (NoAVH group, n = 17)—scoring up to 2. These patients were hallucination free for at least 6 months prior to inclusion in the study. A third group consisted of healthy subjects (Healthy group). Auditory Hallucinations Rating Scale (AHRS) was administered in a group of hallucinating patients to assess the severity of AVHs.

**Stimuli**

During fMRI scanning, the patients performed a metrical stress evaluation task, as described previously. Two-syllable Dutch words appeared on a screen for 2 s, followed by a fixation cross for 3 s. The stimuli were presented in blocks consisting of 12 word-fixation-cross combinations. There were 4 alternating blocks of each condition, lasting for 60 s each, interspersed with a baseline condition (fixation cross) of 30 s. In the first condition, “inner speech,” which initiates phonological processing of imagined speech, the subjects had to indicate whether the metrical stress was located on the first or second syllable by pressing the appropriate response button. Inner speech refers to a common human cognitive process, the vocalization of thoughts, in order to regulate behavior and emotions (eg, commenting to oneself about what is happening, or issuing instructions about what to do). To perform the metrical stress evaluation task, the subjects had to employ this “inner voice” to discriminate the position of stress. A previous fMRI study suggested that this task activates both inner speech production and language perception regions in healthy participants. Half of the stimuli were positive and half negative. Because the subjects were required to make a phonological judgment of the words regardless of their valence, we expect that the valence only contributes to better attention. For half of the stimuli, metrical stress fell on the first syllable and, for the other half, on the second syllable. The second condition involved making a semantic judgment, ie, whether the word presented was positive or negative. Because here we were interested in “inner speech” and not in emotional processing, our analysis was restricted to this condition, compared to the baseline.

**First-Level Data Analysis**

Details of fMRI data acquisition and preprocessing can be found in the Appendix (available online). A contrast per subject was created of the “inner speech” condition vs fixation cross, which yielded reliable activation in the speech area. The contrast of the phonological vs semantic conditions did not show such activation and was therefore considered unsuitable for the purposes of our analysis (ie, to investigate the language network using DCM). The resulting beta-weighted images were used as input in the random effects analysis (RFX) for group
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inferences. The RFX maxima from the contrast served as the basis for time-course extraction (see Appendix, available online) for the DCM analysis (so-called guiding coordinates). Because language processing is lateralized for right-handed people, but not consistently for left-handed people$, only right-handed subjects were considered for DCM analysis.

Effective Connectivity

We tested the hypothesis that disconnections between the frontal and temporal areas and between their left and right hemispheric counterparts underlie the occurrence of hallucinations, as well as aiming to probe the strength of interhemispheric influence. Therefore, we investigated the effective connectivity strengths between 4 regions of interest: Broca’s (B) region, Wernicke’s (W) region, and their homologs in the right hemisphere (BH and WH), using the DCM technique introduced by Friston. Briefly, in DCM, an initial model is created describing (1) the relation between the blood-oxygen-level-dependent (BOLD) response and the 4 regions of interest, (2) the connectivity between these regions, and (3) the modulation of this connectivity induced by the task. The model estimation results in a set of estimated parameter distributions (consisting usually of 10 000 samples) that describe the connectivity strengths between the relevant brain regions, the modulatory influence of the inputs, and the strengths of the inputs, together with the free energy for the model. In most cases in the literature, the mean values calculated from these distributions are used.

We created 64 models for each subject involving the 4 above-mentioned regions of interest: B, W, BH, and WH. All the DCMs assumed bilateral intrahemispherical connections because these connections are usually very strong and varied in all the interhemispherical connections. Four representative models are depicted in figure 1, illustrating the variation between homolog connectivities. For the parallel connections (those between homologs), we assumed that there is always a connection from left to right and studied the feedback from right to left (figure 1; 4 different possibilities). Furthermore, we explored all possible diagonal connections (between B and WH or between W and BH, thus 16 possibilities). These combinations resulted in a total of $4 \times 16 = 64$ models.

The DCMs were then compared using Bayesian model selection (BMS) for each group of subjects separately, yielding the exceedance probability (probability of one model being more likely than the other tested).

Bayesian model averaging (BMA) was used to make inferences on the connectivity strengths between 2 brain regions. BMA summarizes group-specific coupling parameters. It was used to calculate the posterior distributions of the connectivity parameters (consisting of 10 000 samples), which were then used to obtain the posterior means and probabilities.

Bayesian model averaging (BMA) was first calculated per group. The connectivity strengths between the brain regions were compared using a previously described method that combines BMA and a bootstrapping method (for details, see Appendix,
available online). A positive difference in connectivity in more than 95% of the pairs of samples was considered statistically significant.

Next, we averaged models for each subject individually. This step, in addition to the group-level BMA described above, was aimed at investigating subject specificities in the language network. To further evaluate the effect of hallucinations, we performed an ANOVA analysis of the connectivity strengths with respect to groups. This analysis was repeated with respect to gender as a covariate to exclude the possible effect of gender.

Results

fMRI Results and Volume of Interests Guiding Coordinates

The metrical stress task evoked brain activation in all the groups in Broca’s and Wernicke’s regions and their homologs, besides other brain areas such as the anterior cingulate gyrus (family-wise error corrected, figure 1). The random effects general linear model (GLM) for group comparison among healthy participants and the patient groups revealed a number of group differences (supplementary table S1, available online). However, these differences did not survive the correction for multiple comparisons. Guiding coordinates for subsequent VOI extraction were chosen from the group RFX GLM analysis of all participants for the phonological vs fixation cross contrasts (supplementary table S2, available online).

Subjects

Among the initial number of subjects, 18 right-handed healthy subjects and 36 right-handed schizophrenia patients showed significant activation in all 4 brain regions of interest (see section on VOI extraction in Appendix, available online). In this group of patients, 22 had a score on PANSS item P3 of more than 3 and were thus placed in the AVH group. The 3 groups did not differ in age: $F(2,50) = 0.81, P = .45$ (table 1). However, the groups differed in gender: $\chi^2(2,50) = 6.43, P = .04$. Therefore, to exclude the possibility that gender differences produce a confounding effect, we performed the group DCM analysis on the full groups and we additionally controlled the results for the gender of the participants. The groups did not differ by performance, education level, or PANSS symptom severity (table 1). The total AHRS score and the frequency of hallucinations subscale were significantly correlated with the P3 item from PANSS ($r = .688, P = .001; r = .606, P = .005$, respectively).

DCM BMS Results

BMS clearly revealed that the best family was that with bilateral connections between regions on the left hemisphere and their corresponding homologs (Family_1; see figure 1, “Effective Connectivity” subsection of Methods) for all 3 groups (figure 2a). The same result was obtained when the procedure was repeated only for male subjects. However, the BMS for all the models was not fully consistent in all the groups. The best model among all those tested for the healthy group was clearly the full model (belonging to Family_1 and having all the diagonal connections), with an exceedance probability of 96%. For the 2 patient groups, the BMS was less clear. The full model had an exceedance probability of only 62% for the NoAVH group and 80% for the AVH group. This implies that the full model cannot be considered exclusive for the 2 patient groups, even though it is the most probable model among the set that was tested. We may conclude that there are some differences in the BMS between healthy controls and schizophrenia patients for the given set of models.

For the comparison of parameters, the BMA connectivity strengths were randomly sampled from each group and then compared between groups. The distribution of

Table 1. Demographic Data of Subjects

<table>
<thead>
<tr>
<th></th>
<th>Mean (SD)</th>
<th>Significance</th>
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<tbody>
<tr>
<td></td>
<td>Healthy ($n = 18$)</td>
<td>Schizophrenia Patients, NO AVH ($n = 14$)</td>
</tr>
<tr>
<td>Age in years</td>
<td>31 (10)</td>
<td>30 (5)</td>
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<tr>
<td>Gender, males</td>
<td>11</td>
<td>13</td>
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<tr>
<td>Education</td>
<td>4.4 (0.7)</td>
<td>3.7 (1.2)</td>
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<tr>
<td>PANSS pos.</td>
<td>12.5 (4.9)</td>
<td>15.6 (4.1)</td>
</tr>
<tr>
<td>PANSS neg.</td>
<td>13.4 (4.8)</td>
<td>14.7 (5.1)</td>
</tr>
<tr>
<td>PANSS gen.</td>
<td>25.3 (6.2)</td>
<td>28.0 (7.7)</td>
</tr>
<tr>
<td>PANSS tot.</td>
<td>U = 93 (0.34)</td>
<td></td>
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<tr>
<td>Reaction time</td>
<td>1.6 (0.2)</td>
<td>1.6 (0.2)</td>
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<tr>
<td>Accuracy</td>
<td>71.2 (16)</td>
<td>61.5 (12)</td>
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Note: The left column lists the demographic variables. The second to fourth columns from left show average values of the variables across the group and the SD within parentheses. Education level was rated according to a 6-point scale defined by Verhage, which ranges from primary school (1) to university level (6). Nonparametric tests were used to test the group difference for PANSS (Mann-Whitney test), the reaction time and accuracy of the performance (Kruskal-Wallis test), and gender (Chi-square).
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Fig. 2. (a) Results of BMS, showing the exceedance probabilities for healthy controls, schizophrenia patients with no AVH, and schizophrenia patients with AVH. (b) Results of BMA calculated per subject. Each panel is a boxplot (25%–75%) of connectivity strengths for a particular connection (indicated on the panel). Maximal and minimal values are indicated by horizontal bars.

Table 2. Differences Between Posterior Parameters for the Effective Connectivity Calculated by Bootstrapping Between the 3 Groups of Subjects

<table>
<thead>
<tr>
<th></th>
<th>64 Models</th>
<th>B to W</th>
<th>W to B</th>
<th>B to BH</th>
<th>BH to B</th>
<th>W to WH</th>
<th>WH to W</th>
<th>BH to WH</th>
<th>WH to BH</th>
<th>B to BH</th>
<th>W to WH</th>
<th>WH to WH</th>
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<th>B to WH</th>
<th>W to BH</th>
<th>BH to W</th>
<th>WH to B</th>
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<tr>
<td>Probabilities [%]</td>
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<tr>
<td>Healthy – AVH</td>
<td>57</td>
<td><strong>97</strong></td>
<td>36</td>
<td><strong>93</strong></td>
<td>58</td>
<td>55</td>
<td>70</td>
<td>72</td>
<td>67</td>
<td>67</td>
<td>66</td>
<td><strong>94</strong></td>
<td></td>
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<tr>
<td>Healthy – NoAVH</td>
<td>25</td>
<td>82</td>
<td>47</td>
<td>75</td>
<td>61</td>
<td>63</td>
<td>56</td>
<td>57</td>
<td>74</td>
<td>55</td>
<td>58</td>
<td>79</td>
<td></td>
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<tr>
<td>NoAVH – AVH</td>
<td>82</td>
<td>75</td>
<td>39</td>
<td>75</td>
<td>47</td>
<td>41</td>
<td>63</td>
<td>64</td>
<td>39</td>
<td>60</td>
<td>57</td>
<td>74</td>
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<td>Differences of mean [1/s]</td>
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<tr>
<td>Healthy – AVH</td>
<td>0.01</td>
<td><strong>0.11</strong></td>
<td>–0.02</td>
<td><strong>0.09</strong></td>
<td>0.01</td>
<td>0.01</td>
<td>0.03</td>
<td>0.03</td>
<td>0.02</td>
<td>0.02</td>
<td>0.02</td>
<td><strong>0.09</strong></td>
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<tr>
<td>Healthy – NoAVH</td>
<td>–0.04</td>
<td>0.06</td>
<td>0.00</td>
<td>0.04</td>
<td>0.02</td>
<td>0.02</td>
<td>0.04</td>
<td>0.01</td>
<td>0.03</td>
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<td>0.02</td>
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<tr>
<td>NoAVH – AVH</td>
<td>0.05</td>
<td>0.05</td>
<td>–0.02</td>
<td>0.04</td>
<td>–0.01</td>
<td>–0.02</td>
<td>0.02</td>
<td>0.02</td>
<td>–0.01</td>
<td>0.02</td>
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<td>0.04</td>
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<td>Connectivities Mean [1/s]</td>
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<tr>
<td>Healthy</td>
<td>0.44</td>
<td>0.08</td>
<td>0.28</td>
<td>0.07</td>
<td>0.21</td>
<td>0.21</td>
<td>0.17</td>
<td>0.17</td>
<td>0.33</td>
<td>0.18</td>
<td>0.18</td>
<td>0.07</td>
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<tr>
<td>NoAVH</td>
<td>0.47</td>
<td>0.01</td>
<td>0.03</td>
<td>0.03</td>
<td>0.20</td>
<td>0.18</td>
<td>0.17</td>
<td>0.18</td>
<td>0.30</td>
<td>0.17</td>
<td>0.17</td>
<td>0.02</td>
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<tr>
<td>AVH</td>
<td>0.43</td>
<td>–0.03</td>
<td>0.3</td>
<td>–0.01</td>
<td>0.20</td>
<td>0.20</td>
<td>0.14</td>
<td>0.14</td>
<td>0.31</td>
<td>0.16</td>
<td>0.16</td>
<td>–0.02</td>
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Note: The upper columns show the percentage of sample differences for which 1 group had a higher connectivity than the other. A significant difference is considered to be above 95%. Differences with certainty from 90%–95% are considered to have a trend toward significance. The middle columns show the difference of the means of the posterior parameters between groups. The lower columns show the mean posterior parameters for each group. The probabilities and differences showing trend or significance are printed in bold.
parameter differences between the groups was calculated. A significant reduction (table 2) in connectivity strengths was observed in the AVH patients (n = 22) compared to the healthy subjects (n = 18) for the connectivity from W to B (97% of differences were negative), from BH to B (93%), and from WH to B (94%), with reduced connectivity in the hallucinating patients. All the connectivity strengths in the healthy subjects were positive, whereas some of the connection strengths of the AVH group had negative mean values (such as from W to B; see table 2). The connectivity strengths in the NoAVH patients (n = 14) for the same connections were intermediate compared to the other 2 groups but were not significantly different (respective differences of 82%, 75%, and 79% from the healthy group; and 75%, 75%, and 74% from the AVH group).

Next, BMA was calculated for each subject separately, and these values were used for ANOVA analysis (figure 2b). We found an effect of the group on the average connectivity per subject for the connection strengths for W to B (F(2, 51) = 3.300, P = .045) and a trend toward significance for the connection WH to B (F(2, 51) = 2.856, P = .067). Post hoc Bonferroni tests revealed a difference between the connectivity strengths of healthy controls and the AVH group for the W to B connection (P = .04; supplementary table S3a, available online). Because there were unequal numbers of male and female subjects per group, to exclude the possibility that our findings are due to gender-unbalanced groups, the same analysis was repeated including the gender of the participants as a covariate, yielding similar results (supplementary table S3b, available online).

Discussion

Our results point toward reduced connectivity in the frontotemporal language-processing network in schizophrenia patients with AVHs. More specifically, during inner speech, Broca’s area receives reduced input both from Wernicke’s area and from its contralateral homolog in patients with AVH (illustrated in figure 3). Our findings thus lend further support to the frontotemporal disconnection hypothesis of AVH and go beyond that by suggesting directionality. The findings also show that the presence of AVH may be linked to an increased deficit that is present to a lesser degree in those with psychosis, but without current AVH.

Our finding of impaired effective connectivity from other nodes in the speech-processing network (such as Wernicke’s region) to Broca’s region is in agreement with theories of hallucinations that consider that reduced information flow to Broca’s area could prime increased top-down efforts from Broca’s area that are otherwise constrained by perceptual information. According to these theories, top-down connections modulate or sensitize sensory regions through a balance between top-down excitation and inhibition, but they cannot activate the sensory regions under normal conditions. If these top-down signals become tonically hyperactive during a mental disorder, the top-down expectations can give rise to conscious experiences in the absence of bottom-up inputs. A reduced information flow from the speech perception area in the left TPJ implies a loss of feedback to Broca’s area.

Indeed, it has been shown that reduced perceptual input triggers top-down influences in perception, ie, the active search for percepts guided by stored knowledge. With regard to speech processing, an fMRI study showed that only Broca’s area (BA44) was activated by unintelligible speech presented at low signal-to-noise ratios, whereas an extended frontotemporal network (including Broca’s and Wernicke’s areas) was active during intelligible speech at high signal-to-noise ratios. This supports an active role of Broca in trying to make sense of possible speech stimuli in the environment. Reduced information flow may, in everyday life, increase this spontaneous activity of Broca’s area in attempts to “search for relevant information” or “fill in the information gaps” as it were. This may ultimately lead to overactivation of Broca’s and Wernicke’s areas, which is consistent with the overactivation that has
been observed in studies that measured changes in the BOLD signal during hallucinations. Thus, a lack of perceptual input may lead to increased top-down efforts from Broca’s area (top = Broca’s region – higher cognitive processes, down = sensory regions) that are less constrained by perceptual information, as has been hypothesized for hallucinations.

This hypothesis dovetails with the early suggestion of an overly “active listening attitude” in patients with AVH when anticipating meaningful speech. On the other hand, recent evidence from time-resolved sparse fMRI shows that the “top-down” influence of prior knowledge and semantic expectations in speech processing are not necessary from frontal areas to temporal areas but can also be based on feed-forward processing, in which results of lower-level perceptual processing are passed to inferior frontal regions. This would be consistent with the route observed in our study and needs further investigation.

In our study of language processing, we did not explicitly investigate “state” characteristics of brain activity during hallucinations but instead invoked the language areas within a language network. Therefore, we did not expect overactivation of Broca’s area in AVH patients during the task, which may be suppressed by controlled task-related activity during an experimental inner speech paradigm. This is in agreement with the results of a recent meta-analysis that compared the findings of so-called trait studies with studies investigating the brain activation of AVH patients in different “states” (during the hallucination period vs the nonhallucination period). Consistent overactivation of Broca’s region was found during hallucinations, a feature that was not observed in “trait” studies.

Furthermore, patients without hallucinations were found to have connectivity strengths in between patients with hallucinations, who had the lowest connectivity coefficients, and the healthy controls. It should be noted, however, that the “nonhallucinating” group contained people who did not have current hallucinations at the time of scanning, but they may have had AVH in the past. Therefore, it is a reasonable assumption that rather than representing dichotomous categories, our patient groups are actually on a continuum, where the AVH group may display a stronger or more acute deficit compared to the non-AVH group.

Our finding of impaired effective connectivity from Wernicke’s region to Broca’s region is difficult to compare with the so-called corollary discharge hypothesis. Recent experimental studies point toward a delay in top-down control (from Broca’s to Wernicke’s area), which is not straightforward to investigate using either DCM or fMRI data.

A second finding of our study concerned the reduced connectivity between Broca’s area and its homolog, which should be interpreted with caution because it was only marginally significant. This may be associated with the emotional content of hallucinations, as the right IFG has been implied in emotional aspects of speech. Indeed, our task employed words with emotional connotations. It has been suggested that a lack of synchronization between both areas may lead to the erroneous interpretation of emotional speech activity from the right hemisphere as coming from an external source. Interestingly, for both areas that show reduced information flow to the left IFG (left TPJ and right IFG), reduced gray matter volumes have been reported in relationship to hallucinations, reviewed in Allen et al. Allen et al. (2008) suggested that Broca’s homolog may show reduced connectivity with Broca’s area, thereby hampering adequate speech monitoring.

We are aware of only 1 previous study that investigated effective connectivity in relationship to hallucinations in schizophrenia, using a verbal self-monitoring task involving distorted speech. The authors found reduced connectivity from the left STG to the anterior cingulate (an area consistently involved in self-monitoring). Although the task used was clearly different, using external speech, and engaged a different brain circuit, the results are consistent with our findings regarding a reduced information flow from posterior temporal to frontal regions in patients with hallucinations. Our study has the advantage that the subjects had to engage their own inner speech to perform the task, which may be a more appropriate proxy to the processes involved in AVH.

Other studies of functional connectivity and hallucinations have mainly focused on the resting state and did not investigate directionality. Nevertheless, most findings implicate language-related areas. For example, Vercammen et al. reported reduced connectivity of the left TPJ with the ACC and amygdala, in association with AVH severity in schizophrenia, using resting-state fMRI. No patients without hallucinations were included. When patients were compared to healthy control subjects, reduced connectivity between the left TPJ and right IFG was observed, 2 nodes that were also implicated in our current analyses. Another recent study of functional connectivity in the resting state reported elevated connectivity between Wernicke’s region, its homolog, and the left IFG in schizophrenia patients with hallucinations as compared to patients without hallucinations, but not in comparison to healthy control subjects. These variable results may be explained by the absence of a specific task, where it remains unclear which cognitive processes are reflected in the interaction between language network nodes. Furthermore, these studies did not clarify whether the connectivity changes reflected “downstream” effects from Broca or “upstream” effects from Wernicke to Broca. A clear advantage of the current study is the task-based theoretical framework of a priori regions and directional influences in addition to taking into account the nature of the hemodynamic response, which might account for different findings.
Our results are consistent with anatomical connectivity studies investigating both the interhemispheric pathways between language areas, involving the anterior corpus callosum, and the pathways connecting the frontal areas and the superior temporal areas such as the arcuate fasciculus, which is part of the superior longitudinal fasciculus. These studies found an association of auditory hallucinations with abnormalities in fractional anisotropy in these pathways.

Our findings also point toward more generalized changes in language circuitry, ie, differences that may be attributable to schizophrenia rather than the presence and/or severity of hallucinations. In other words, the full model had much lower exceedance probability in both groups of schizophrenia patients as compared to controls. This is indicative of differences between the healthy controls and schizophrenia patients in the brain network that was tested and it suggests differences in the language-processing pathways of healthy controls and schizophrenia patients. In particular, the model with the next-best fit lacked a connection from Wernicke's homolog to Broca's area, indicating that the connection from Wernicke's homolog to Broca's area might be diminished in both groups of schizophrenia patients.

**Limitations**

We used DCM, which is a modeling technique based on a preexisting hypothesis. The main limitation is that the number of regions has to be predefined by the hypothesis, thus it is not used to explore all possible nodes of the putative network. We limited our investigation to well-established language-related brain regions. Thus, even though the ACC is coactivated along with other regions in this task, it was excluded from our model. Indeed, the ACC's role has been investigated with respect to hallucinations using tasks that engage self-monitoring processes. Furthermore, DCM incorporates hemodynamic responses for each region and each subject separately, such that regional hemodynamic variations do not prevent the estimation of neuronal coupling parameters. This is especially useful when comparing different groups, as in our study, where some subjects can display a different hemodynamic response due to factors such as medication intake. Another limitation is that our conclusions are limited to processing differences associated with having recently experienced hallucinations (in the week prior to scanning). Patients in the nonhallucinating group did not experience hallucinations in the 6 months prior to scanning. However, they may have experienced hallucinations earlier in their illness, and thus may still have trait characteristics associated with hallucinations. Future research should further disentangle state and trait characteristics by including patients who have never experienced hallucinations, even though such patients may be difficult to find.

In summary, our results point toward a reduced connectivity between frontal and temporal language areas in schizophrenia patients with AVH. A reduced information flow from the speech perception area in the left TPJ may lead to a loss of feedback and increased top-down efforts that are less constrained by perceptual information from Broca's area, as has been hypothesized for hallucinations. Finally, the reduced information flow from Broca's right hemispheric homolog, which engages during emotional and nonliteral speech processing, may isolate emotional language activity in the right hemisphere. It may thus eventually acquire an “independent” nature, due to a failure of integration into normal language processing, reflecting the emotional non-self content of hallucinations.

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**Supplementary Material**

Supplementary material is available at http://schizophreniabulletin.oxfordjournals.org.

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**References**


