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Running head: HALLUCINATIONS IN SCHIZOPHRENIA

Left-dominant temporal-frontal hypercoupling in schizophrenia patients with hallucinations during speech perception

Katie M. Lavigne[1,2], Lucile A. Rapin[3], Paul D. Metzak[1,2], Jennifer C. Whitman[1,2], Kwanghee Jung[4], Marion Dohen[5], Hélène Lœvenbruck[6] & Todd S. Woodward[1,2*]

[1]Department of Psychiatry, University of British Columbia, Vancouver, BC, Canada

[2]BC Mental Health and Addictions Research Institute, Provincial Health Services Authority, Vancouver, BC, Canada

[3] Department of Linguistics, Université du Québec à Montréal, Montréal, Québec

[4] Department of Pediatrics, University of Texas Health Science Center, Houston, TX, USA

[5] Speech and Cognition Department, Grenoble University, Grenoble, France

[6] LPNC, CNRS UMR 5105, Univ. Grenoble Alpes, France

*Address correspondence to Todd S. Woodward, Ph.D., BC Mental Health & Addictions Research Institute, Room 117, 3rd Floor, 938 W. 28th Avenue, Vancouver, B.C., Canada. V5Z 4H4. E-mail: todd.woodward@ubc.ca. Phone: 604-875-2000 x 4724. Fax: 604-875-3871.

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Abstract

Background: Task-based functional neuroimaging studies of schizophrenia have not yet replicated the increased coordinated hyperactivity in speech-related brain regions that is reported with symptom-capture and resting-state studies of hallucinations. This may be due to suboptimal selection of cognitive tasks. *Methods:* In the current study we used a task that allowed experimental manipulation of control over verbal material, and compared brain activity between 23 schizophrenia patients (10 hallucinators, 13 non-hallucinators), 22 psychiatric (bipolar) and 27 healthy controls. Two conditions were presented, one involving inner verbal thought (in which control over verbal material was required) and another involving speech perception (in which control verbal material was not required). *Results:* A functional connectivity analysis resulted in a left-dominant temporal-frontal network that included speech-related auditory and motor regions, and showed hypercoupling in past-week hallucinating schizophrenia patients (relative to non-hallucinating patients) during speech perception only. *Conclusions:* These findings replicate our previous work showing generalized speech-related functional network hypercoupling in schizophrenia during inner verbal thought and speech perception, but extend them by suggesting that hypercoupling is related to past-week hallucination severity scores during speech perception only, when control over verbal material is not required. This result opens the possibility that practicing control over inner verbal thought processes may decrease the likelihood or severity of hallucinations.

KEYWORDS: SCHIZOPHRENIA, INNER SPEECH, SPEECH PERCEPTION, FUNCTIONAL MAGNETIC RESONANCE IMAGING, FUNCTIONAL CONNECTIVITY

Introduction

Auditory verbal hallucinations (AVHs) are speech perceptions that occur in the absence of an external stimulus. They are a predominant feature of schizophrenia, and typically occur out of the control of the patient. Symptom capture studies investigating the hallucinatory state have reported hyperactivity in a network of speech-related brain regions while patients are actively hallucinating (e.g., primary and secondary auditory cortices, Broca's area, frontal operculum, hippocampus and parahippocampal region) relative to periods of no hallucinations[1-5]. Resting-state studies have also reported increased activation[6] and connectivity[7] in fronto-temporal regions in hallucinating compared to non-hallucinating schizophrenia patients and healthy controls.

Expansion of these symptom-capture and resting-state findings to task-based functional neuroimaging is important for identifying the *cognitive functions* underlying this increased activity/connectivity, and thereby contributing to cognitive-based theories about the genesis of AVHs. However, task-based functional neuroimaging studies often do not report whether or not activity/connectivity is increased in patients experiencing hallucinations in the past week[(e.g., 8, 9)]. This methodology leads to difficulties in determining whether differences are specifically related to the presence of AVHs, the diagnosis of schizophrenia, or to psychiatric disorders more generally (when comparisons are made to healthy control subjects only). In addition, the seminal work in this area has focused on inclusion of a willful inner speech (or auditory imagery) condition[8, 10], but no hallucination-associated hyperactivity/hypercoupling has emerged under those conditions (although decreased activity has). It has been argued that inclusion of a willful auditory imagery condition diverges somewhat from the experience of hallucinating patients[11], since when hallucinating patients are asked to imagine speech cast in another person's voice or

one of their previously heard "voices", the patient will not experience the result as a hallucination[12]. This is because only unbidden experiences can be interpreted as hallucinations[11]. Thus, since AVHs occur out of the control of the patient, experimental manipulation of control over verbal material should be important for understanding the functional biology of hallucinations.

Such an experimental manipulation can be achieved in straightforward fashion through comparison of willful inner speech (i.e., voluntary verbal thought generation; VTG) to speech perception (SP) conditions[13]. Inner speech, also called silent-speech, covert-speech, or verbal thought, can be defined as silent speech production in one's own mind[14, 15]. A subtype of inner speech is the deliberate generation of silent coherent verbal material, or verbal thought, which activates the so-called task-positive brain network[13, 16]. This type of voluntary inner speech is to be contrasted with the less willful "mind wandering", in which verbal thoughts are also mentally expressed, but in a less deliberate fashion, and which activates brain regions within the task-negative (or default mode) network[16, 17]. In the present study we use the term voluntary verbal thought generation to describe an intended conscious production of inner speech in response to a stimulus. During VTG, participants exert some degree of control over verbal material as they are required to mentally generate definitions of common words. SP, however, does not require control over verbal material, as participants simply listen to pre-recorded definitions. A preliminary study by our group using this comparison revealed coordinated hyperactivity/hypercoupling[1] in a temporal-frontal network of speech-related auditory and motor

[1] It is important to note that a clear distinction between *coordinated hyperactivity* and *hypercoupling* is not available with functional connectivity analyses. Brain regions with correlated and strong activations over time, which emerge on the same functional network (e.g., as a result of singular value decomposition or component analysis), can be thereby considered coupled, and do so because they increase and reduce activation in synchrony (i.e., in a

regions for schizophrenia patients relative to healthy controls during both VTG and SP[13]; however, it was not possible to examine differences between hallucinating and non-hallucinating schizophrenia patients due to a small sample. The goal of the present study was to extend our previous work by investigating whether this hypercoupling is associated with hallucination ratings in schizophrenia patients, and whether exertion of control over verbal material affects brain activity within this network in hallucinating patients.

In accordance with our past work, we expected that schizophrenia patients, irrespective of hallucination status, would demonstrate hypercoupling in a temporal-frontal network including auditory and motor regions. We further expected that hypercoupling in this functional network would be higher in hallucinating schizophrenia patients for the SP condition (in which there is assumed to be little control over verbal material) relative to non-hallucinating schizophrenia patients, psychiatric, and healthy controls.

Methods and Materials

Participants

Participants were 23 schizophrenia patients (10 hallucinators; H_SZ; 13 non-hallucinators; NH_SZ), 22 non-hallucinating bipolar patients (BP), and 27 healthy controls (HC), all of whom had been using English daily for at least the past 5 years and responded accurately to questions about the consent form designed to confirm their ability to read and understand English. Most were right-handed[18] (n=65; Left-handed = 2 HCs; Mixed = 1 HC, 1 NH_SZ, 3 BPs). Both in- and outpatients were included in the patient samples. Bipolar patients were

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coordinated fashion) over time. Highly coordinated and strong increases and decreases in activity lead to higher intercorrelations between regions, and can be interpreted as coordinated hyperactivity and/or hypercoupling. Therefore, we use the two terms interchangeably here.

selected as a psychiatric control group due to the similarities between people with a diagnosis of bipolar disorder and people with a diagnosis of schizophrenia with regards to cognitive, genetic and environmental susceptibility factors[19]. Therefore, any aspect of task performance attributable to these factors (or other overlapping characteristics, such as the stigmatization associated with mental illness) should be present for individuals within both groups. A hearing test was carried out on all but one participant using an audiometer (AMBCO 650AB, www.ambco.com) to ensure absence of hearing impairment. All participants provided written informed consent and met magnetic resonance imaging compatibility criteria. The study was approved by both the University of British Columbia (UBC) and UBC Hospital Clinical Research Ethics Committees and participants received financial compensation of $10 CAD per hour and reimbursement of travel costs for participation. Details regarding demographic variables can be found in the Supplementary Material.

Patients' symptoms were assessed using the Signs and Symptoms of Psychotic Illness scale (SSPI[20]; see Table 1 for means and group differences). The SSPI consists of 30 items and is criterion referenced, providing specific examples of behaviour (over the past week) which correspond to severity levels for each item (e.g., Hallucinations: 0 = absent; 1 = vague descriptions of hallucinations; 2 = hallucinations which the patient accepts as arising from within his/her own mind; 3 = definite hallucinations occurring occasionally (e.g. < once/day); 4 = definite hallucinations which are frequent and/or influence observable behaviour). For the following analyses, schizophrenia patients were included in the hallucinating and non-hallucinating subgroups based on their SSPI Hallucinations score (hallucinating: 3 (n = 3) or 4 (n = 7; non-hallucinating: 0 (n = 9), 1 (n = 2) or 2 (n=2)). All hallucinating patients reported auditory hallucinations, and 6 patients reported multimodal hallucinations (tactile = 6; visual = 3;

olfactory = 1). All schizophrenia patients but one had experienced hallucinations in the past. All bipolar patients scored 0 on hallucinations, with the exception of one who was rated 2 (visual hallucinations only).

Task

The task design employed here was nearly identical to that used in our previous study[13], with adjustments in stimulus timing, presentation, and the addition of a post-scan questionnaire to provide evidence that definitions were in fact generated. Briefly, participants were presented with a noun (object) and its corresponding image (e.g., Pillow) and instructed to either mentally generate (VTG) or to listen to (SP) a simple definition of the word (e.g., "Something you rest your head on when sleeping"). The two experimental conditions were presented in blocks consisting of 15 trials each (30 trials total for each condition across two runs), with a 60s rest break in between the two conditions. Stimuli were randomly assigned to each condition for each participant separately. The conditions were cued with the words "something you…" and "listen…" presented under the images in the VTG and SP conditions, respectively (see Figure 1; see Supplementary Material for details on stimulus presentation and timing). Participants were administered a post-scan questionnaire where they were asked, for each trial, whether they generated a definition and, if so, what that definition was. Patients were also asked whether they experienced AVHs during fMRI scanning; one schizophrenia patient reported auditory hallucinations during testing, and this occurred during both conditions.

Data Analysis

fMRI data analysis was carried out using constrained principal component analysis for fMRI (fMRI-CPCA; www.nitrc.org/projects/fmricpca) with orthogonal rotation[21-26]. Details on

image acquisition, image preprocessing, and data analysis procedures are presented in the Supplementary Material.

Results

Inspection of the scree plot[27, 28] suggested that two components should be extracted. Both Components 1 and 2 showed a significant effect of Peristimulus Time, $F(8,568) = 77.63$, $p < .001$; $F(8,568) = 95.78$, $p < .001$, respectively, and visual inspection of the predictor weights confirmed a hemodynamic response (HDR) shape. The percentages of task-related variance accounted for by each rotated component were 17.91%, and 7.97% for components 1 and 2, respectively.

Anatomical Descriptions

The brain regions associated with Component 1 are displayed in Figure 2A (top panel; red/yellow), with anatomical descriptions in Table S2 of the Supplementary Material. Component 1 was characterized by a network of voxel clusters dominated by activations in regions involved in language production and comprehension including pars opercularis of the left inferior frontal gyrus (BA 44) and bilateral superior temporal gyri (BAs 21, 22), as well as activations within bilateral visual/fusiform regions (BAs 17, 18, 19, 37), and supplementary motor area (BA 6). The brain regions associated with Component 2 are displayed in Figure 2A (top panel; blue/green), with anatomical descriptions in Table S3. Component 2 was characterized by a functional network involving increased activity in bilateral visual/fusiform regions (BAs 18, 19, 37) overlapping with those from Component 1, and decreased activity in regions overlapping with the default mode or task-negative network[16, 29], such as posterior cingulate cortex and precuneus (BA 23), medial prefrontal (BAs 9, 10), superior frontal (BA 8),

and inferior parietal/lateral occipital cortex (BA 39, 40), as well as decreased activity in other regions such as precentral gyrus (BA 6) and superior parietal cortex (BAs 2, 5, 7).

Relation to Experimental Conditions

A 2 x 9 x 2 x 4 mixed-model ANOVA revealed a significant Condition × Peristimulus Time × Group interaction, $F(24, 544) = 2.24$, $p < .001$, $\eta_p^2 = 0.09$, but no significant 4-way interaction ($p > .8$). This suggests that, with respect to understanding Group differences, the HDR shape (indexed by peristimulus time) and Condition must be taken into account, but Components 1 and 2 can be combined, as is displayed in Figure 2. In order to interpret this interaction, we examined group differences at each time bin for each condition separately, averaged over both components.

Observation of effect sizes in simple-simple main effects characterizing the significant Condition × Peristimulus Time × Group interaction demonstrated that, as is clear in Figure 2B, the largest effects are observable when comparing hallucinating schizophrenia patients to the other three groups in SP: (1) relative to controls at time bin 1, $F(1,68) = 17.84$, $p < .001$, $\eta_p^2 = 0.21$, time bin 2, $F(1,68) = 12.34$, $p < .005$, $\eta_p^2 = 0.15$, time bin 3, $F(1,68) = 6.03$, $p < .05$, $\eta_p^2 = 0.08$, and time bin 9, $F(1,68) = 4.77$, $p < .05$, $\eta_p^2 = 0.07$; (2) relative to bipolar patients at time bin 1, $F(1,68) = 10.14$, $p < .005$, $\eta_p^2 = 0.13$, time bin 2, ($F(1,68) = 7.02$, $p < .05$, $\eta_p^2 = 0.09$, time bin 3, $F(1,68) = 4.04$, $p < .05$, $\eta_p^2 = 0.06$, time bin 7, $F(1,68) = 5.04$, $p < .05$, $\eta_p^2 = 0.07$, and time bin 8, $F(1,68) = 4.93$, $p < .05$, $\eta_p^2 = 0.07$; and (3) relative to non-hallucinating schizophrenia patients at time bin 1, $F(1,68) = 6.54$, $p < .05$, $\eta_p^2 = 0.09$, time bin 2, $F(1,68) = 4.13$, $p = .05$, $\eta_p^2 = 0.06$, time bin 7, $F(1,68) = 4.63$, $p < .05$, $\eta_p^2 = 0.06$, time bin 8, $F(1,68) = 5.23$, $p < .05$, $\eta_p^2 = 0.07$, and time bin 9, $F(1,68) = 6.39$, $p < .05$, $\eta_p^2 = 0.09$. Non-hallucinating schizophrenia

patients showed greater intensity relative to controls for time bin 6, $F(1,68) = 6.53$, $p < .05$, $\eta_p^2 = 0.09$, with no other group contrasts reaching significance for SP.

In addition, as is clear in Figure 2C, the largest effects are observable when comparing schizophrenia patient groups to healthy and psychiatric controls in VTG: hallucinating schizophrenia patients demonstrated greater intensity relative to healthy controls at time bin 3, $F(1,68) = 4.48$, $p < .05$, $\eta_p^2 = 0.06$, and time bin 4, $F(1,68) = 6.60$, $p < .05$,$\eta_p^2 = 0.09$, and non-hallucinating schizophrenia patients demonstrated significantly greater intensity relative to controls at time bin 4, $F(1, 68) = 8.37$, $p < .01$, $\eta_p^2 = 0.11$, time bin 5, $F(1, 68) = 10.47$, $p < .005$, $\eta_p^2 = 0.13$, and time bin 6, $F(1, 68) = 5.33$, $p < .05$, $\eta_p^2 = 0.07$, as well as relative to bipolar patients at time bin 5, $F(1,68) = 3.92$, $p = .05$, $\eta_p^2 = 0.06$. All increases in intensity can be interpreted as greater activation increases in red areas in Figure 2A, and greater activation decreases in blue areas in Figure 2A.

Correlation with Hallucinations

In order to examine associations with hallucinations, correlations were computed between the estimated HDR (i.e., predictor weights) for each condition and the SSPI hallucinations item for schizophrenia patients. The estimated HDR was averaged across time bins 1, 2, and 3 for SP and time bins 3 and 4 for VTG, given that these were the time points on which hallucinating schizophrenia patients were distinguishable from controls, for each condition respectively. The SSPI Hallucinations score was significantly correlated with the estimated HDR in the SP condition, $r(21) = 0.46$, $p < .05$, and not in the VTG condition, $r(21) = 0.11$, $p > .60$; however, the difference between these correlations did not reach statistical significance, $Z = 1.20$, $p < .24$. Scatterplots for both of these correlations are presented in Supplementary Material (Figures S1 and S2 for SP and VTG, respectively). None of the

remaining 19 SSPI categories were significantly related to the estimated HDR in either SP or VTG using a cutoff of significance of $p = .01$ in accordance with the exploratory nature of those correlations (see Table S4 of the Supplementary Material for the full list of correlations).

Discussion

Functional neuroimaging studies have reported hyperactivity in speech-related brain networks in hallucinating schizophrenia patients during the experience of hallucinations[1-5] as well as at rest[6, 7]. However, task-based functional neuroimaging studies have not yet demonstrated that this increased activity/connectivity is associated with hallucinations in schizophrenia. In the current event-related fMRI study, we examined task-elicited activity during conditions requiring (VTG) or not requiring (SP) control over verbal material in schizophrenia patients with and without hallucinations, bipolar patients, and healthy controls. Functional connectivity analysis revealed a left-dominant temporal-frontal network including speech-related auditory and motor regions, which showed hypercoupling in hallucinating schizophrenia patients relative to all other groups during SP. In addition, this hypercoupling was higher in both hallucinating and non-hallucinating schizophrenia patients relative to controls and bipolar patients during VTG. These findings replicate our previous work showing generalized speech-related functional network hyperactivity in schizophrenia during inner verbal thought and speech perception[13], but extend them by suggesting that hypercoupling is related to hallucination scores only during speech perception, when control processes are not required.

The finding of hypercoupling in hallucinating schizophrenia patients when control processes are not required fits with the observation that AVHs occur out of the control of the patient[30]. The involvement of the superior temporal gyrus (STG) provides further evidence that bottom-up cognitive processes contribute to hallucinations, in accordance with a number of

neurocognitive accounts of AVHs[11, 31-34]. However, the results also suggest that top-down influences may play an important role, because the expectation of control over verbal material in VTG negated the hallucination-specific hypercoupling observed in SP. The nature of the interplay between top-down and bottom-up influences seems fertile ground for future research on AVHs, and have already been considered by other accounts as efference copy[11,34], or expectations, hypervigilance, imagination/fantasy, and memories/trauma[35]. Another possible top-down influence on hallucinations is the cognitive biases underlying delusions, such as hypersalience of a match between evidence (increased vividness of perceptual qualities) and a self-selected hypothesis ("I will hear voices")[36-38].

The hypercoupling observed in both hallucinating and non-hallucinating schizophrenia patients in VTG can be explained by the reduced cognitive efficiency account of schizophrenia as a diagnostic category[39]. Assuming that the requirement for cognitive control in VTG requires more cognitive capacity than in SP, it is important to note that people with schizophrenia are known to demonstrate reduced efficiency in functional networks, whereby, relative to healthy controls, they must devote more cognitive resources to perform a moderately demanding task[22, 39, 40]. Therefore, increased engagement of these functional networks would be expected regardless of hallucination severity, since inefficiency is thought to be diagnosis-based and not symptom-based[22, 39, 40].

Interestingly, the current results provide evidence that the hypercoupling for hallucinating schizophrenia patients relative to the other groups in SP was present during task-off periods; namely, in the period between 0-5 seconds post stimulus, when the HDR should not have had sufficient time to increase in response to task demands. Although brain activity during task-off periods reflects a wide range of cognitive processes[41, 42], this hypercoupling in hallucinating

schizophrenia patients in the current study was observed in the same network involved in the task-on period, suggesting that this particular task-off activity engages the same networks as SP. Note that an HDR shape with a sharp peak would not be expected during task-off periods (as it is for task-on periods) because the cognitive processes occurring during task-off periods do not have consistent timing. This suggests that for hallucinating patients during the off-task period of the SP block (1) a functional network that includes speech-related auditory and motor regions is more active, which has been suggested elsewhere for auditory cortex[43], and (2) the deactivation of the default-mode network normally associated with task-related activity is already pronounced, as has been suggested for schizophrenia patients[44]. Importantly, this effect was not present during VTG, which differed from the SP condition in that it involved the added expectation of exerting control over verbal material. This suggests that, for schizophrenia patients with hallucinations, the expectation of exerting cognitive control attenuated the abnormalities found during task-off periods; namely, it attenuated both exaggerated activation of temporal-frontal regions, and exaggerated reduction of default-mode regions. From this we can speculate that expecting to control inner verbal thought processes may reduce hypercoupling in the speech-related functional network, and reduce the likelihood of hallucinations. The suggestion that control processes and hallucinations are incompatible has already been proposed by the breakaway speech/unbidden thoughts account of hallucinations[11, 31-33].

It has been previously stated that AVHs may be attributable to fronto-temporal disconnection[10, 45, 46], possibly resulting from a breakaway speech perception network[31-33]. However, with the current set of results we provide evidence for hypercoupling in a left-dominant temporal-frontal network associated with AVHs during speech perception. The participants with the highest estimated HDR peaks (suggesting hypercoupling) were the

schizophrenia patients experiencing the most severe hallucinations in the previous week (in SP). Additional evidence for coordinated hyperactivity/hypercoupling (as well as other connectivity concepts) may be achieved by combining structural measures of connectivity with functional measures, such as measures of white matter integrity (e.g., diffusion tensor imaging; DTI). For example, DTI studies have supported the notion of increased connectivity between language and auditory processing regions in patients with AVHs, but have also provide evidence for fronto-temporal disconnection[47-49].

Limitations of this study include an absence of direct quantification of trial-by-trial task engagement. However, given that all group differences involved *increased* activity for schizophrenia patients relative to controls, it is unlikely that the results were influenced by patients being disengaged from the task. It was also not possible to discount the influence of cognitive processes occurring between the offset of the auditory stimulus and the onset of the ITI in SP, which lasted just over 2 seconds; however, given the similarities between the shape of the estimated HDRs in SP and VTG, it is unlikely that cognitive processes during this period affected the current results. In addition, an alternative interpretation of the absence of an association with hallucinations during VTG is a noisier signal in that condition, since the thought processes in VTG have more variable timing than the perceptual processes in SP. Another limitation is that, to the extent the cognitive processes studied here are affected by antipsychotic medication, the current results could be confounded by medication use, as dosage was not available for all participants. Finally, it was not possible in the current study to determine whether the hypercoupling observed during SP in hallucinating schizophrenia patients is specific to speech, or is a more general effect. If hyperactivity in this network were specific to AVHs, one

would not expect to see similar hyperactivity during a non-speech auditory task. Further research will be needed in order to investigate these alternative possibilities.

Conclusion

The goal of the present study was to determine whether hallucination-associated task-based hypercoupling in a speech-related auditory-motor network depends on the engagement of control processes. Schizophrenia patients demonstrated hypercoupling in a left-dominant temporal-frontal network involving auditory-motor brain regions under conditions both requiring (VTG) and not requiring (SP) control over verbal material. Importantly, this effect was associated with hallucination ratings only for speech perception, when control processes were not engaged, suggesting that the expectation of exerting cognitive control led to a correction of hypercoupling in recently hallucinating patients. This result opens the possibility that practicing control over inner verbal thought processes may decrease the likelihood or severity of hallucinations, a finding that may be an important consideration for cognitive behavioural therapy (CBT) for voice-hearing[50-52].

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The authors have declared that there are no conflicts of interest in relation to the subject of study.

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Table 1. Signs and Symptoms of Psychotic Illness (SSPI) means and standard deviations (SD; in parentheses) for patient groups.

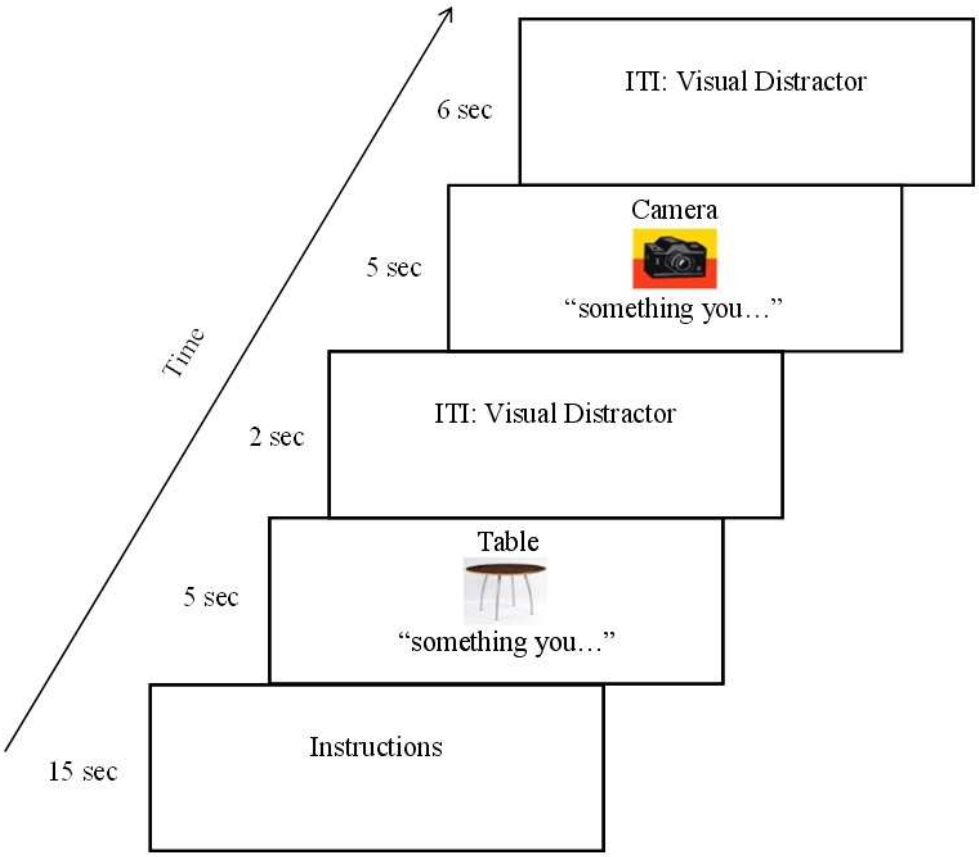
Variable	Bipolar (BP)		Schizophrenia – NonHallucinating (NH_SZ)		Schizophrenia – Hallucinating (H_SZ)	
	Mean (SD)	**Range**	**Mean (SD)**	**Range**	**Mean (SD)**	**Range**
Anxiety	1.45 (1.22)	0-4	1.08 (1.26)	0-3	1.70 (0.82)	1-3
Depression	1.14 (1.36)	0-4	0.85 (1.21)	0-3	1.60 (1.26)	0-3
Anhedonia	1.09 (1.34)	0-4	0.92 (0.95)	0-3	1.30 (1.25)	0-3
Elated Mood	0.64 (1.00)	0-3	0.54 (0.88)	0-2	0.30 (0.67)	0-2
Insomnia	1.18 (1.33)	0-4	1.08 (1.44)	0-4	0.70 (1.06)	0-3
Somatic Complaints	0.18 (0.39)	0-1	0.15 (0.38)	0-1	0.30 (0.95)	0-3
Delusions[a]	0.64 (1.22)	0-4	1.46 (1.39)	0-4	3.00 (0.82)	2-4
Hallucinations[a]	0.09 (0.43)	0-2	0.46 (0.78)	0-2	3.70 (0.48)	3-4
Attentional Impairment	1.41 (0.73)	0-2	1.54 (0.88)	0-3	1.40 (0.97)	0-3
Disorientation	0	0	0.08 (0.28)	0-1	0.20 (0.42)	0-1
Overactivity	1.00 (0.87)	0-2	1.15 (1.14)	0-3	0.80 (1.03)	0-3
Underactivity	0.86 (1.04)	0-3	1.38 (1.12)	0-3	1.60 (1.17)	0-3
Flattened Affect[b]	0.55 (0.91)	0-3	1.54 (1.20)	0-3	1.60 (0.97)	0-3
Inappropriate Affect	0	0	0.23 (0.83)	0-3	0.10 (0.32)	0-3
Pressure of Speech	0.14 (0.35)	0-1	0.15 (0.38)	0-1	0.20 (0.63)	0-2
Poverty of Speech	0.14 (0.47)	0-2	0.31 (0.48)	0-1	0.50 (0.71)	0-2
Disordered Form of Thought	0	0	0.46 (0.97)	0-3	0.20 (0.63)	0-2
Peculiar Behaviour	0.09 (0.29)	0-1	0.15 (0.38)	0-1	0.30 (0.95)	0-3
Irritability/Hostility	0.27 (0.46)	0-1	0.46 (0.97)	0-3	0.50 (0.71)	0-2
Impaired Insight[c]	0.67 (1.06)	0-4	0.92 (1.38)	0-4	1.90 (0.99)	0-3

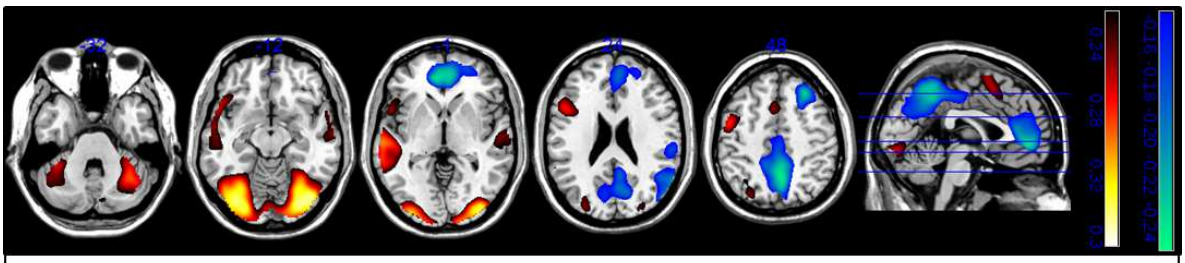
Note. [a] : H_SZ > NH_SZ & BP, $p < .01$; [b] : BP < H_SZ & NH_SZ, $p < .01$; [c] : BP < H_SZ, $p < .01$

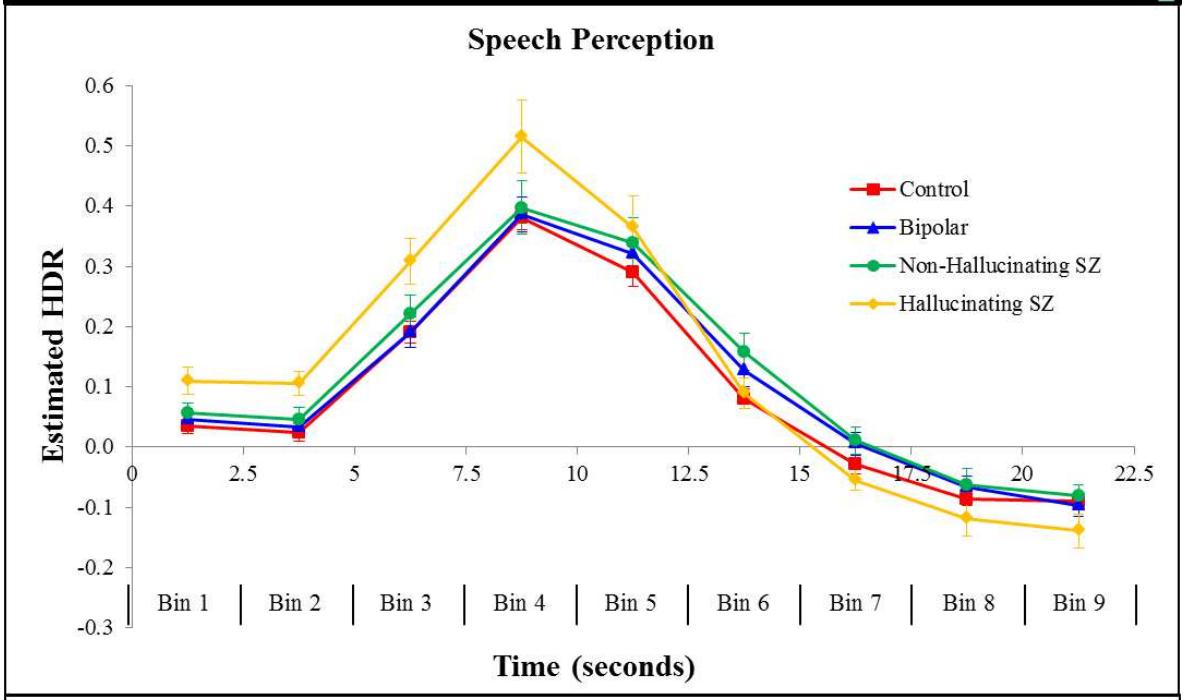
Figure Legends

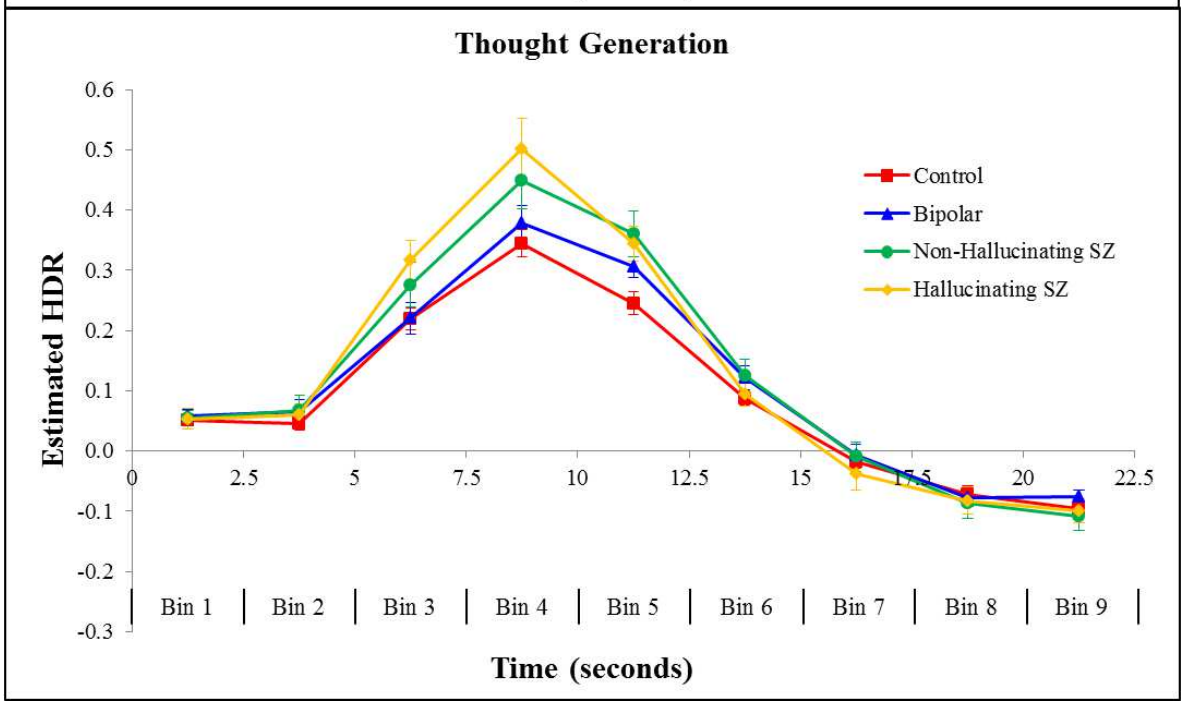
Figure 1. Timeline of the experimental procedure. Participants were instructed to either mentally generate (VTG) or to listen to (SP) a simple definition of a word (e.g., "Something you rest your head on when sleeping" for the word "Pillow"). The conditions were cued with the words "something you…" or "listen…" presented under the images for the VTG and SP conditions, respectively. The VTG condition is depicted here.

Figure 2 A-C. A: Dominant 10% of component loadings for Component 1 (red/yellow = positive loadings; threshold = .20, max = .37, no negative loadings passed threshold) and Component 2 (blue/green = negative loadings, negative threshold = -.14, min = -.25). Component 2 positive loadings in the occipital regions overlapped with those from Component 1 (see Tables S2 and S3). Axial slices are located at Montreal Neurological Institute Z-axis coordinates -32, -12, -1, 24, 48. B: Mean finite impulse response (FIR)-based predictor weights for speech perception (SP), averaged over components and plotted as a function of peristimulus time. C: Mean FIR-based predictor weights for voluntary verbal thought generation (VTG), averaged over components and plotted as a function of peristimulus time. Error bars are standard errors. HDR = Estimated Hemodynamic Response; L = Left; R = Right; SZ = Schizophrenia.


Time
15 sec
Instructions
5 sec
Table
"something you…"
2 sec
ITI: Visual Distractor
5 sec
Camera
"something you…"
6 sec
ITI: Visual Distractor




Speech Perception
Estimated HDR
0.6
0.5
0.4
0.3
0.2
0.1
0.0
-0.1
-0.2
-0.3
0
2.5
5
7.5
10
12.5
15
17.5
20
22.5
Control
Bipolar
Non-Hallucinating SZ
Hallucinating SZ
Bin 1
Bin 2
Bin 3
Bin 4
Bin 5
Bin 6
Bin 7
Bin 8
Bin 9
Time (seconds)


Thought Generation
Estimated HDR
0.6
0.5
0.4
0.3
0.2
0.1
0.0
-0.1
-0.2
-0.3
0
2.5
5
7.5
10
12.5
15
17.5
20
22.5
Control
Bipolar
Non-Hallucinating SZ
Hallucinating SZ
Bin 1
Bin 2
Bin 3
Bin 4
Bin 5
Bin 6
Bin 7
Bin 8
Bin 9
Time (seconds)

Left-dominant temporal-frontal hypercoupling in schizophrenia patients with hallucinations during speech perception

Supplementary Material

Participants

A one-way ANOVA testing for group differences on common demographic variables (see Table S1 for group means) revealed a significant difference in age, $F(3,71) = 5.35$, $p < .005$. Least significant difference (LSD) post-hoc comparisons confirmed that the bipolar group was significantly older than controls and hallucinating schizophrenia patients, with no other group differences reaching significance. IQ was evaluated using the Kaufman Brief Intelligence Test version 2 (K-BIT-2)[1] and the Wechsler Test of Adult Reading (WTAR)[2]. All but three schizophrenia patients (1 never medicated, 1 previously medicated, and 1 missing) were on antipsychotic medication at the time of testing. All but four bipolar patients were taking anti-depressants (3 never used, 1 past use) and 11 were taking antipsychotic medication. Although a significantly smaller number of bipolar patients were on antipsychotic medication relative to hallucinating, χ^2 (1, N = 32) = 5.66, $p < .05$, and non-hallucinating, χ^2 (1, N = 32) = 10.12, $p < .05$ schizophrenia patients, the two schizophrenia groups did not differ from each other ($p > .05$). Although dosage was not available for all participants taking anti-psychotic medication, chlorpromazine equivalent dosage was computed for 7 hallucinating and 5 non-hallucinating schizophrenia patients. Means comparisons indicated no significant differences on dosage between these two groups ($p > .05$). DSM-IV-TR[3] diagnoses on referral were confirmed using the Mini-International Neuropsychiatric Interview (MINI)[4]. The exclusion criteria for all groups included history of neurological disorder, traumatic brain injury with loss of consciousness for more than 5 minutes and any cognitive sequalae resulting from loss of consciousness, or

diagnosis of substance abuse/dependence. History of psychiatric disorder (self or immediate family) warranted exclusion for the control group.

Stimuli

Three 30-word lists of nouns were created using the MRC psycholinguistic database[5]. In order to facilitate generation of definitions, only nouns with values greater than 500 on familiarity, concreteness, and imageability criteria ratings were chosen (maximum value = 700). The three word lists (i.e., list A, B and C) were matched by mean values on these parameters. All nouns were objects of neutral affective content within the categories of food, houseware, furniture, clothing, and transportation devices. Audio stimuli were recorded by a female native speaker of English in a quiet room and lasted on average 2.22 seconds (SD = 0.62). Two out of the three word lists were randomly assigned to the two conditions for each participant separately, leading to six potential combinations of word sets (i.e., AB, BA, AC, CA, CB, and CB), which were counterbalanced across participants.

Prior to fMRI scanning, participants were familiarized with the experimental procedure in a computerized practice run, using 10 words (5 VTG, 5 SP) different from those presented in the scanner. In order to facilitate generation of definitions while in the scanner, participants also practiced audibly generating definitions for the 30 words in the VTG condition, with no time limit imposed. No specific training was carried out for the SP material to ensure that familiarity with the material would not increase the likelihood of self-generating definitions during this condition. During fMRI scanning, the two experimental conditions were displayed using Presentation Software 12.1 (http://www.neurobs.com). For each condition, each word, its associated illustration, and the condition cue, were displayed for five seconds. Words were written in white in a 48 point Times New Roman font and presented on a black background. The

illustration was placed under the word and the display was centered on screen (see Figure 1 in the main text). In the SP condition, the audio file containing the definition was presented 700 ms after the onset of the word and illustration. The provided definitions always began with the words "Something you" and participants were instructed that mentally generated definitions should also start with "Something you", in order to ensure that at least some words were mentally generated on every trial, and to minimize any interpretational confounds between conditions.

In order to prevent participants from internally reviewing the most recently generated or heard definition, a display of generic circles moving in an orbiting motion was presented during the inter-trial interval (ITI). The distribution of the duration of the ITI was exponential, optimizing the deconvolution of the blood oxygenation level dependent (BOLD) signal (mean=4.46s, range=2s, 4, 6, 8, 16, 20s)[6]. The order of presentation of the ITIs, conditions, and words within each block were randomized.

Image Acquisition and Processing

Imaging was performed at the University of British Columbia MRI Research Centre on a Philips Achieva 3.0 Tesla (T) MRI scanner with quasar dual gradients (maximum gradient amplitude, 80mT/m; maximum slow rate, 200 mT/m/s). The participant's head was firmly secured using a customized head holder. Functional image volumes were collected using a T2*-weighted gradient-echo spin pulse sequence with 36 axial slices; thickness/gap, 3/1 mm; matrix, 80×80; repetition time (TR), 2500 ms; echo time (TE), 30 ms; flip angle (FA), 90°, field of view (FOV), 240×240 mm, effectively covering the whole brain. 352 images were acquired over two runs of approximately 7 min and 30 s each.

Functional images were pre-processed using Statistical Parametric Mapping 8 (SPM8; Wellcome Trust Centre for Neuroimaging, UK). For each participant, each functional run was realigned, co-registered to their structural (T1) image, and subsequently normalized to the Montreal Neurological Institute (MNI) T1 brain template. All images were spatially smoothed with an 8x8x8 mm full width at half maximum Gaussian filter.

Connectivity Analysis

fMRI data analysis was carried out using constrained principal component analysis for fMRI (fMRI-CPCA) with orthogonal rotation[7-11]. The theory and proofs for CPCA are detailed in previously published work[12, 13]. The fMRI-CPCA application is available on-line, free of charge (www.nitrc.org/projects/fmricpca). fMRI-CPCA computes components representing functional brain networks on BOLD signal for which variance has been constrained (using multivariate multiple regression) to be predictable from task timing. This application of CPCA involved preparation of two matrices. The first matrix, *Z*, contained the BOLD time series of each voxel, with one column per voxel and one row per whole brain scan. Each column contained the realigned, co-registered, normalized and smoothed activations over all scans, for each subject separately. The second matrix, *G* (design matrix), contained finite impulse response (FIR) models of the expected BOLD response to the timing of stimulus presentations.

Preparation of G

The *G* (design) matrix consisted of a FIR basis set, which can be used to estimate the increase in BOLD signal at specific peristimulus scans relative to all other scans. The value 1 is placed in rows of *G* for which BOLD signal amplitude is to be estimated, and the value 0 in all other rows ("mini boxcar" functions). The time bins for which a basis function was specified in the current study were the 1st to 9th scans following stimulus presentation. Since the repetition

time (TR) for these data was 2.5 s, this resulted in estimating BOLD signal over a 22.5 s window, with the start of the first time bin (time = 0) corresponding to encoding stimulus onset. In this analysis we created a *G* matrix that would allow us to estimate subject-and-condition specific effects by inserting a separate FIR basis set for each condition and for each individual subject. The columns in this subject-and-condition based *G* matrix code 9 peristimulus time bins, 2 conditions (VTG and SP), and 72 subjects, resulting in 1296 columns ($9 \times 2 \times 72 = 1296$).

Matrix Equations

The matrix of BOLD time series and design matrices are taken as input, with BOLD in *Z* being predicted from the FIR model in *G*. In order to achieve this, multivariate least-squares linear regression was carried out, whereby the BOLD time series (*Z*) was regressed onto the design matrix (*G*):

$$Z = GC + E, \quad (1)$$

where $C = (G'G)^{-1}G'Z$, or least squares multivariate multiple regression. This analysis yielded condition-specific regression weights in the *C* matrix (i.e., regression weights specific to the experimental conditions as defined by the design matrix). The condition-specific regression weights are often referred to (in conventional fMRI analyses) as beta images. *GC* contained variability in *Z* that was predictable from the design matrix *G*, that is to say, variability in *Z* that was predictable from the timing of stimulus presentations.

The next step employed singular value decomposition (SVD) to extract components representing networks of functionally interconnected voxel activations from *GC*. This involved singular value decomposition of the activation variability that was predictable from the design matrix (*GC*):

$$UDV' = GC \quad (2)$$

where *U* = matrix of left singular vectors; *D* = diagonal matrix of singular values; *V* = matrix of right singular vectors. Each column of *VD* can be overlaid on a structural brain image to allow visualization of the brain regions involved in each functional network. In the current application of CPCA, following dimension reduction, we orthogonally rotated[7] and rescaled the *VD* matrix prior to display, so that a rotated loading matrix is displayed. The values of the loading matrix contain the correlations between the components in *U* and the variables in *GC*. The orthonormal rotation transformation matrix is then used to transform the rescaled left singular vectors *U* into rotated component scores (with rows corresponding to scans).

Predictor Weights

To interpret the components with respect to the conditions represented in *G*, we produced predictor weights in matrix *P*. These are the weights that would be applied to each column of the matrix of predictor variables (*G*) to create *U* (*U*=*GP*) and can be orthogonally rotated by applying the same transformation matrix[7] as was applied to *VD* and *U*. The values in *P* indicate the importance of each column in the *G* matrix to the network(s) represented by the component(s) in *VD*, so are essential for relating the resultant components to the experimental conditions of interest represented in *G*. This approach estimates a hemodynamic response (HDR) shape for each individual separately, so fully accommodates heterogeneity in HDRs.

Data Analysis

These predictor weights, which provide estimates of the engagement of functional networks at each point in peristimulus time, can be used to statistically test the effect of peristimulus time to determine whether or not these values are reflecting a hemodynamic response (HDR) shape (and not simply varying randomly around zero). A significant effect of peristimulus time combined with a biologically plausible HDR shape provides evidence that the

component is reflecting a reliable BOLD response to the stimuli[7-9]. These analyses were carried out as 2 × 9 × 2 × 4 mixed model ANOVAs, with the within-subjects factors of Component (2 components were extracted from the CPCA), Peristimulus Time (9 whole-brain scans after the onset of each stimulus were estimated in the finite impulse response model), Condition (SP vs. VTG), and the between-subjects factor of Group (hallucinating schizophrenia patients, nonhallucinating schizophrenia patients, bipolar patients, and healthy controls). Any impact of group or condition would typically be reflected by a significant interaction with peristimulus time for the measure of estimated HDR (i.e., the predictor weights), although main effects are also possible. Tests of sphericity were carried out for all ANOVAs, and adjustment in degrees of freedom for violations of sphericity did not affect the results; therefore, the original degrees of freedom are reported.

Table S1. Group means (standard deviations in parentheses) for demographic variables.

Variable	Control	Bipolar	Schizophrenia - NonHallucinating	Schizophrenia - Hallucinating
N	27	22	13	10
Sex (% female)	40.70	45.50	53.80	40.00
Age	28.89 (8.98)	40.05 (10.77)	33.23 (9.85)	31.90 (9.62)
Education	15.57 (1.86)	14.36 (1.89)	14.31 (1.84)	14.20 (3.61)
K-BIT Vocab	101.04 (11.97)	96.57 (8.95)	103.91 (11.41)	100.20 (17.03)
K-BIT Matrices	108.81 (12.82)	105.67 (12.82)	113.42 (15.40)	107.30 (12.61)
K-BIT Composite	105.70 (9.29)	101.24 (9.71)	110.45 (13.49)	104.50 (14.90)
WTAR	40.44 (5.49)	36.73 (7.41)	40.15 (7.50)	36.00 (12.53)

Note. K-BIT = Kaufman Brief Intelligence Test; WTAR = Wechsler Test of Adult Reading.

Table S2. Cluster volumes for the most extreme 10% of Component 1 loadings, with anatomical descriptions, Montreal Neurological Institute (MNI) coordinates, and Brodmann's area (BA) for the peaks within each cluster.

Cortical Regions	**Cluster Volume**		**BAs for Peak Locations**	**MNI Coordinate for Peak Locations**			**Loading Value**
	voxels	**(mm^3)**		**x**	**y**	**z**	
Cluster 1: Bilateral	16717	133736					
Temporal Occipital Fusiform Cortex			37	32	-52	-20	0.37
Temporal Occipital Fusiform Cortex			37	-32	-50	-22	0.37
Temporal Occipital Fusiform Cortex			19	-30	-62	-18	0.37
Occipital Fusiform Gyrus			19	-38	-64	-18	0.37
Lateral Occipital Cortex, Inferior Division			19	40	-76	-14	0.34
Lateral Occipital Cortex, Inferior Division			18	28	-86	6	0.33
Lateral Occipital Cortex, Inferior Division			18	-28	-88	4	0.31
Occipital Pole			18	16	-94	-4	0.29
Lingual Gyrus			17	0	-84	-14	0.28
Lingual Gyrus			18	-8	-90	-16	0.27
Lateral Occipital Cortex, Superior Division			7	-28	-70	44	0.24
Cluster 2: Left Hemisphere	5628	45024					
STG, Posterior Division			21	-58	-24	0	0.30
STG, Posterior Division			22	-60	-38	4	0.29
Inferior Frontal Gyrus, Pars Opercularis			44	-48	14	30	0.28
Temporal Pole			38	-54	14	-4	0.27
Precentral Gyrus			6	-48	4	44	0.27
Cluster 3: Right Hemisphere	1310	10480					
STG, Anterior Division			22	60	-10	-2	0.27
STG, Anterior Division			38	58	6	-8	0.25
STG, Posterior Division			21	60	-30	4	0.23
STG, Posterior Division			22	52	-34	6	0.22
Cluster 4: Bilateral	308	2464					
Superior Frontal Gyrus			6	-4	12	56	0.25
Supplementary Motor Area			6	-2	6	62	0.23
Cluster 5: Left Hemisphere	128	1024					
Thalamus			27	-18	-28	-4	0.23
Cluster 6: Right Hemisphere	21	168					
Thalamus			27	18	-28	-4	0.21

Note. STG = Superior Temporal Gyrus

Table S3. Cluster volumes for the most extreme 10% of Component 2 loadings, with anatomical descriptions, Montreal Neurological Institute (MNI) coordinates, and Brodmann's area (BA) for the peaks within each cluster.

Cortical Regions	**Cluster Volume**		**BAs for Peak Locations**	**MNI Coordinate for Peak Locations**			**Loading Value**
	voxels	**(mm^3)**		**x**	**y**	**z**	
Positive Loadings							
Cluster 1: Right Hemisphere	3378	27024					
Occipital Pole			18	30	-90	4	0.25
Occipital Fusiform Gyrus			19	34	-68	-16	0.23
Temporal Occipital Fusiform Cortex			37	34	-50	-20	0.22
Cluster 2: Left Hemisphere	2914	23312					
Lateral Occipital Cortex, Inferior Division			19	-26	-90	0	0.24
Occipital Fusiform Gyrus			19	-34	-64	-18	0.22
Occipital Fusiform Gyrus			18	-26	-78	-16	0.21
Temporal Occipital Fusiform Cortex			37	-32	-48	-22	0.21
Negative Loadings							
Cluster 1: Bilateral	8334	66672					
Precuneus Cortex			23	2	-52	52	-0.25
Cingulate Gyrus, Posterior Division			23	4	-24	44	-0.20
Precuneus Cortex			18	-8	-70	22	-0.18
Superior Parietal Lobule			7	26	-48	64	-0.18
Superior Parietal Lobule			2	32	-44	64	-0.18
Superior Parietal Lobule			5	22	-50	64	-0.18
Superior Parietal Lobule			2	-26	-44	62	-0.17
Precentral Gyrus			6	-18	-14	62	-0.16
Superior Parietal Lobule			5	-22	-50	64	-0.16
Angular Gyrus			40	44	-52	58	-0.15
Superior Parietal Lobule			40	42	-50	60	-0.15
Cluster 2: Right Hemisphere	4605	36840					
Middle Frontal Gyrus			9	26	32	46	-0.23
Cingulate Gyrus, Anterior Division			32	4	44	14	-0.23
Superior Frontal Gyrus			8	26	10	60	-0.17
Frontal Pole			10	22	54	14	-0.17
Middle Frontal Gyrus			8	28	12	58	-0.16
Frontal Pole			46	22	52	20	-0.16
Superior Frontal Gyrus			6	26	0	62	-0.16
Precentral Gyrus			6	30	-8	62	-0.15
Cluster 3: Right Hemisphere	4245	33960					

Lateral Occipital Cortex, Superior Division			39	44	-76	36	-0.21
Angular Gyrus			39	50	-58	20	-0.21
Supramarginal Gyrus, Anterior Division			2	58	-28	34	-0.19
Supramarginal Gyrus, Anterior Division			48	56	-28	30	-0.18
Supramarginal Gyrus, Posterior Division			40	60	-36	36	-0.18
Cluster 4: Left Hemisphere	332	2656					
Lateral Occipital Cortex, Superior Division			19	-42	-82	32	-0.16
Lateral Occipital Cortex, Superior Division			39	-54	-74	20	-0.16
Cluster 5: Left Hemisphere	242	1936					
Middle Frontal Gyrus			9	-26	34	38	-0.18
Cluster 6: Left Hemisphere	16	128					
Supramarginal Gyrus, Anterior Division			48	-60	-30	26	-0.15

Table S4. Correlations between Signs and Symptoms of Psychotic Illness (SSPI) symptom ratings categories and estimated hemodynamic response (HDR) for schizophrenia patients in speech perception (SP) and voluntary verbal thought generation (VTG).

Variable	Schizophrenia (SZ)	
	SP	VTG
Anxiety	-0.09	-0.26
Depression	0.06	0.17
Anhedonia	0.24	0.44*
Elated Mood	-0.20	-0.16
Insomnia	-0.34	-0.30
Somatic Complaints	-0.02	0.02
Delusions	0.32	-0.20
Hallucinations	0.46*	0.13
Attentional Impairment	-0.03	-0.05
Disorientation	0.30	-0.24
Overactivity	-0.39	-0.44*
Underactivity	-0.03	-0.11
Flattened Affect	-0.04	-0.16
Inappropriate Affect	-0.14	-0.06
Pressure of Speech	-0.15	-0.30
Poverty of Speech	0.19	0.24
Disordered Form of Thought	-0.11	-0.26
Peculiar Behaviour	0.04	-0.06
Irritability/Hostility	0.02	-0.17
Impaired Insight	0.03	-0.01

Note. * = $p < .05$; Estimated HDR averaged over time bins 1 to 3 for SP, and 3 to 4 for VTG.

Figure S1. Scatterplot of the correlation between Signs and Symptoms of Psychotic Illness (SSPI) hallucinations rating and estimated hemodynamic response (HDR) for speech perception (SP) averaged across time bins 1 to 3.

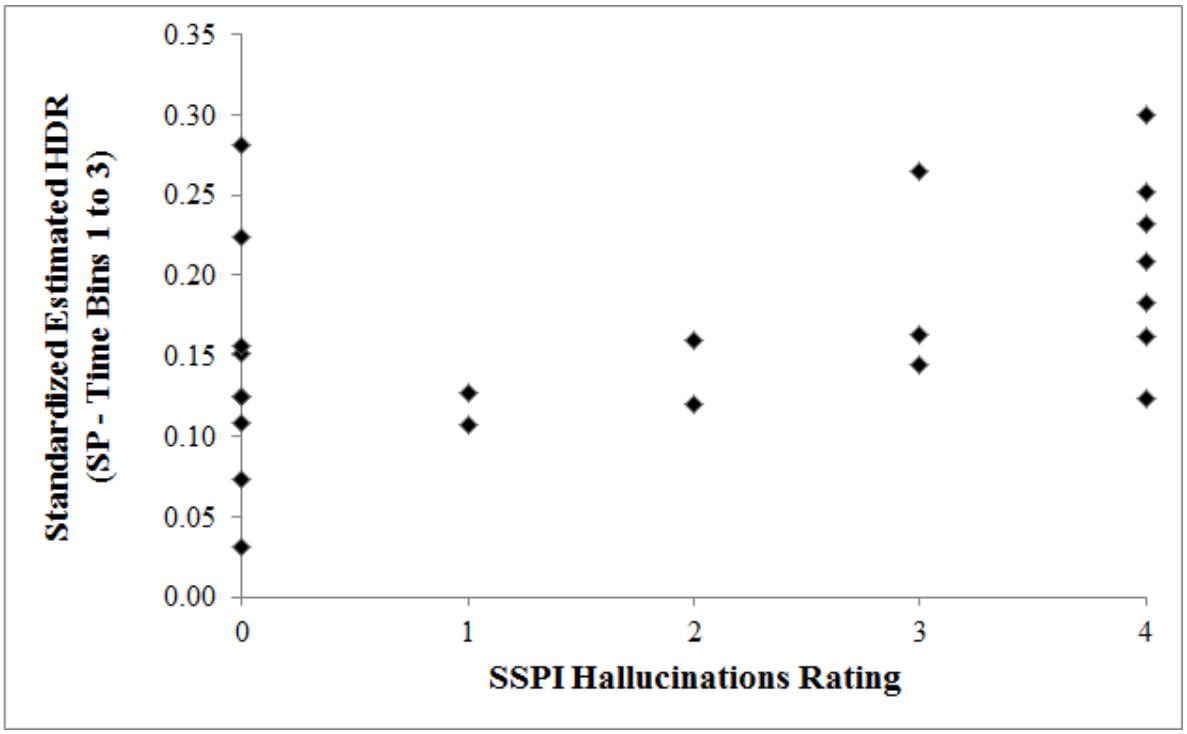
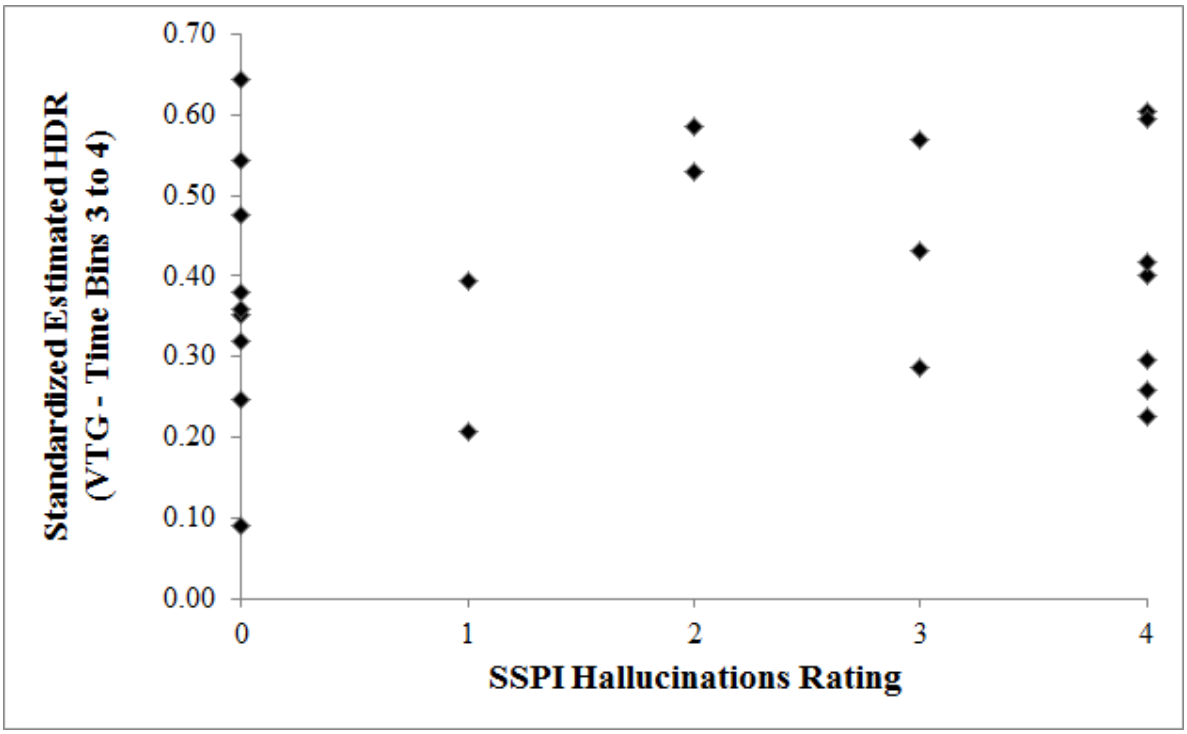


Figure S2. Scatterplot of the correlation between Signs and Symptoms of Psychotic Illness (SSPI) hallucinations rating and estimated hemodynamic response (HDR) for voluntary verbal thought generation (VTG) averaged across time bins 3 to 4.



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