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Hallucination- and speech-specific hypercoupling in frontotemporal auditory and language networks in schizophrenia using combined task-based fMRI data: an fBIRN study

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Abstract

Hypercoupling of activity in speech-perception-specific brain networks has been proposed to play a role in the generation of auditory-verbal hallucinations (AVHs) in schizophrenia; however, it is unclear whether this hypercoupling extends to non-verbal auditory perception. We investigated this by comparing schizophrenia patients with and without AVHs, and healthy controls, on task-based functional magnetic resonance imaging (fMRI) data combining verbal speech perception (SP), inner verbal thought generation (VTG), and non-verbal auditory oddball detection (AO). Data from two previously-published fMRI studies were simultaneously analyzed using group constrained principal component analysis for fMRI (group fMRI-CPCA), which allowed for comparison of task-related functional brain networks across groups and tasks while holding the brain networks under study constant, leading to determination of the degree to which networks are common to verbal and non-verbal perception conditions, and which show coordinated hyperactivity in hallucinations. Three functional brain networks emerged: (1) auditory-motor, (2) language processing, and (3) default-mode (DMN) networks. Combining the AO and sentence tasks allowed the auditory-motor and language networks to separately emerge, whereas they were aggregated when individual tasks were analyzed. AVH patients showed greater coordinated activity (deactivity for DMN regions) than non-AVH patients during SP in all networks, but this did not extend to VTG or AO. This suggests that the hypercoupling in AVH patients in speech-perception-related brain networks is specific to perceived speech, and does not extend to perceived non-speech or inner verbal thought generation.

Keywords

AUDITORY-VERBAL HALLUCINATIONS; SPEECH PERCEPTION; AUDITORY ODDBALL; FUNCTIONAL BRAIN NETWORKS; CONNECTIVITY

Coordinated hyperactivity or hypercoupling[1] in speech-perception-related brain regions has been implicated in the generation of auditory-verbal hallucinations (AVHs) in schizophrenia.

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Studies examining functional brain activity during the experience of hallucinations have reported activation of language and auditory regions (e.g., Broca's area, middle/superior temporal gyri (Allen, et al., 2012; Jardri, et al., 2011)), findings which are supported by network-based connectivity analyses (Hoffman, et al., 2011b; Thoma, et al., 2016). Trait studies, in which functional brain activity is compared between patients with and without a history of AVHs, have also demonstrated hypercoupling/coordinated hyperactivity within auditory/language networks in AVH patients at rest (Alderson-Day, et al., 2016; Shinn, et al., 2013); however, findings of task-based trait studies are less consistent (Ćurčić-Blake, et al., 2017), with some reporting hypoactivity (Kompus, et al., 2011), suggesting interference between AVHs and external auditory processing (Hugdahl, 2015), and others reporting hyperactivity in similar regions (Hoffman, et al., 2011a; Lavigne, et al., 2015b). These equivocal findings are likely due to differences in the tasks and statistical analysis techniques employed. In a previous study, we observed hypercoupling during speech perception (SP) in AVH patients relative to non-AVH patients within a network of speech-related brain regions (e.g., bilateral superior temporal gyri, left inferior frontal gyrus) consistent with symptom capture and resting state studies. This hypercoupling in AVH patients was not observed during inner verbal thought generation (VTG), suggesting that it is not present when control is exerted over verbal material, as with inner speech (Lavigne, et al., 2015b; Rapin, et al., 2012).

Several theoretical accounts of AVHs also point to hyperactivity in speech-related brain regions as a contributing factor. Ford & Hoffman (2013; Hoffman, et al., 2011a) proposed that spontaneous activation of verbal imagery results in AVHs due to a hyperconnected corticostriatal loop (left inferior frontal gyrus, Wernicke's area and right homologue, and bilateral putamen) in combination with top-down factors in the form of efference copy (Ford, et al., 2007). Several other theories highlight the importance of hypersensitivity of auditory cortex as a bottom-up process involved in the generation of AVHs, either as a primary feature (e.g., breakaway speech/unbidden thoughts; Hoffman, 1999; Hoffman, 2010), or as a factor involved in the interplay between top-down and bottom-up processes (Aleman and Vercammen, 2013; Ćurčić-Blake, et al., 2017).

Given the verbal nature of most auditory hallucinations, this hyperactivity may be specific to perception of verbal material. This should be tested by directly comparing functional brain activity between patients with and without AVHs during contrasting verbal and non-verbal auditory perception tasks. In the current study, we investigated this by combining already-available data: one set from our laboratory involving the verbal sentence task (SP and VTG conditions) described above (Lavigne, et al., 2015b), and another from the publicly available Function Biomedical Informatics Research Network (fBIRN) phase II multisite study involving a non-verbal auditory oddball (AO) task (Friedman, et al., 2008; Keator, et al., 2008). The auditory oddball task is commonly used in schizophrenia research on attention and salience detection (Kim, 2014), and is a theoretically interesting comparison condition

[1]A clear distinction between coordinated hyperactivity and hypercoupling is not possible 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 considered coupled, and do so because they increase and reduce activation in a coordinated fashion over time. Highly coordinated and strong increases/decreases in activity lead to higher intercorrelations between regions, and can be interpreted as coordinated hyperactivity and/or hypercoupling. These terms are, therefore, used interchangeably.

because it requires auditory perception in the absence of a verbal component. That is, there are two aspects of speech perception that might contribute to hyperactivity in auditory (and language) regions in AVHs, the verbal component and the auditory component. VTG includes the verbal, but not auditory, component, whereas AO includes the auditory, but not verbal, component of SP. Simultaneous investigation of these three tasks provides a means of examining the speech-specificity of hyperactivity in auditory and language networks in AVHs.

We have previously published analyses of these two datasets separately (Lavigne, et al., 2016; Lavigne, et al., 2015b), and found an association with hallucinations for the verbal speech perception task (Lavigne, et al., 2015b), but not the non-verbal AO task (Lavigne, et al., 2016), providing preliminary support for the proposition that hyperactivity is specific to verbal material. However, comparing these two results in this indirect fashion is not conclusive because different brain networks emerged in the two studies. Ideally, the brain networks under study would be held constant, and activation in the associated hemodynamic response (HDR) shapes could be compared between tasks and groups. We have previously developed methodology to do this (Lavigne, et al., 2015a), but in that work compared two versions of the same task, not two tasks with different perceptual content.

This task-combination methodology and patient-group comparison involved using group constrained principal component analysis for functional magnetic resonance imaging (group fMRI-CPCA; Hunter and Takane, 2002; Metzak, et al., 2011; Takane and Shibayama, 1991; Woodward, et al., 2016; Woodward, et al., 2015) on the combined dataset. This allows identification of the degree to which functional brain networks are involved in all task conditions, provides spatial and temporal information for each network, and allows statistically-based group comparisons of HDR response shapes. For the current study, based on our past work (Lavigne, et al., 2016; Lavigne, et al., 2015b), we expected to identify auditory and language processing networks, and hypothesized that schizophrenia patients with AVHs, relative to those without and healthy controls, would show hypercoupling in both of these networks for SP, but not for VTG (no overt language perception) or AO (nonverbal material), which would confirm that hyperactivity specific to perceived speech-related brain regions plays a role in AVHs in schizophrenia.

Methods

Participants

Participants were schizophrenia patients and healthy controls from two functional magnetic resonance imaging (fMRI) datasets. The first dataset consisted of 27 healthy controls, 11 non-AVH, and 12 AVH schizophrenia patients who performed a verbal sentence task including speech perception and inner verbal thought generation conditions (Lavigne, et al., 2015b). Mean illness duration was 14.05 years (SD = 10.14), and all but one patient was currently taking antipsychotic medication. Nineteen patients were taking an atypical antipsychotic, and two were taking a typical antipsychotic, as their primary medication. Fourteen patients were also taking a second antipsychotic medication (2 typical, 12 atypical), and four were taking a third atypical medication (1 missing data). Chlorpromazine equivalent dosages were available for 14 patients: mean = 1018.57; SD = 2402.92.

Symptoms were assessed using the Signs of Symptoms of Psychotic Illness (SSPI; Liddle, et al., 2002), which is scored on a 5-point scale corresponding to severity of hallucinations (0 = absent, 1 = vague descriptions of hallucinations, 2 = hallucinations that the patient accepts as arising from within his/her own mind, 3 = definite hallucinations occurring occasionally [e.g., < once/day], 4 = definite hallucinations that are frequent and/or influence observable behaviour). Patients scoring greater than 2 on the hallucinations item were included in the AVH group. All patients experienced AVHs (i.e., voices), though two also experienced other auditory hallucinations, such as auditory distortions, simple noises, and music. Six patients also experienced multimodal hallucinations (6 tactile, 3 visual, 1 olfactory). All participants were screened for MRI compatibility and gave written informed consent prior to participation. Experimental procedures were approved as part of a larger study by the University of British Columbia clinical research ethics board.

The second dataset was acquired from the publicly available fBIRN phase II multisite study (Friedman, et al., 2008), which consists of data collected at six sites across the United States of America: Duke/UNC, Brigham and Women's Hospital, Massachusetts General Hospital, University of California – Irvine, University of New Mexico, and Yale. Data were downloaded from the fBIRN Data Repository, Project Accession Number 2007-BDR-6UHZ1. The quality-controlled data set (see Lavigne, et al., 2016) included 50 healthy controls, 23 non-AVH, and 35 AVH patients diagnosed with schizophrenia or schizoaffective disorder who completed an auditory oddball task. Patients' symptoms were assessed using the Scale for the Assessment of Positive Symptoms (SAPS; Andreasen, 1984), which is scored on a six-point scale from 0 to 5 in increasing severity: 0 = none; 1 = questionable; 2 = mild (noises or single words, which only appear occasionally); 3 = moderate (clear evidence of voices occurring at least weekly); 4 = marked (clear evidence of voices occurring almost daily); 5 = severe (voices occur often daily). As with the sentence task sample, patients scoring greater than 2 on the hallucinations item were included in the AVH group. Observation of scores on the SAPS items Voices Commenting and Voices Conversing confirmed that most hallucinating patients experienced AVHs; however, the presence of AVHs could not be confirmed in eight patients who reported auditory hallucinations, as the AVH-specific items were not endorsed or were scored below the same cut-off value of 2. Nineteen patients also reported multimodal hallucinations (10 somatic-tactile, 6 olfactory, 13 visual). All patients were stable and had no changes in their medications in the two months prior to testing; however, additional information regarding medication and illness history was not available, which precluded us from comparing the two samples on these measures. All fBIRN sites received local Institutional Review Board approval.

Table 1 shows demographic information for each group, for the auditory oddball and sentence tasks separately. There were no significant differences between groups on age, gender or handedness for either task.

Experimental Design

Sentence Task—Participants were presented with a noun (object) and its corresponding image (e.g., Table) and instructed to either listen to (speech perception condition; SP) or mentally generate (inner verbal thought generation condition; VTG) a simple definition of

the word (e.g., “Something you eat dinner on”; see Figures 1A and 1B, respectively). The SP and VTG conditions were presented in blocks consisting of 15 trials each (30 trials total for each condition across two runs), with an inter-trial interval (ITI) between stimuli, and a 60s rest break between the two conditions. The ITI was exponential to optimize deconvolution of the blood oxygenation level dependent (BOLD) signal (Serences, 2004), and lasted from 2 to 20s (mean = 4.46s). Stimuli were randomly assigned to each condition for each participant separately. The conditions were cued with the words “listen…” and “something you…” presented under the images in the SP and VTG conditions, respectively, in order to ensure that at least some words were mentally generated on every trial, and to minimize any interpretational confounds between conditions. Following the experiment, participants were asked whether or not they experienced hallucinations during the scanning session. One patient reported active AVHs during the speech perception trials, and one patient reported tactile hallucinations during the thought generation trials (data were missing for two subjects).

fBIRN Auditory Oddball Task—The two-tone AO task (Figure 1C) involved listening to a series of tones and indicating with a button press when a target tone (i.e., a tone deviating in frequency) was presented. Four runs of the auditory oddball task were completed in each of two sessions, leading to a total of eight runs per subject that each lasted 280s. Each run began with 15s of silence, followed by a series of tones lasting 100ms each, with 500ms interstimulus intervals between them; a 15s period of silence indicated the end of each run. The majority of the tones (standard tones; 95% occurrence) were presented at a frequency of 1000Hz and the remaining tones (target tones; 5% occurrence) were presented at a frequency of 1200Hz. The latency between two target tones varied between 6s and 15s, allowing for deconvolution of the BOLD signal (Serences, 2004). Auditory stimuli were presented binaurally through headphones. Prior to the functional scan, participants adjusted right and left ear volumes to a test stimulus to ensure the tones could be heard over scanner noise. Participants were instructed to focus on a black fixation cross displayed on a grey screen throughout the run, and to respond with a button press when they heard the target tone. Stimuli were presented using E-Prime software (http://www.pstnet.com/products/e-prime/). After the experiment, patients were asked whether they experienced hallucinations during the scanning session, with one patient reporting AVHs “almost constantly”, one “occasionally”, and one reporting visual hallucinations occasionally (data were missing for 11 subjects).

Image Acquisition and Processing

Imaging for the sentence task data was performed at the University of British Columbia MRI Research Centre using a Philips Achieva 3.0 Tesla (T) MRI scanner with quasar dual gradients (maximum gradient amplitude, 80mT/m; maximum slew 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.

Imaging for the fBIRN data was performed at five sites (one site was excluded during quality control; Lavigne, et al., 2016) across the United States of America, for which imaging parameters were matched as closely as possible based on preliminary testing (Friedman, et al., 2008; Magnotta and Friedman, 2006): 27 slices if possible; thickness/gap = 4mm/1mm; matrix = 64×64; repetition time (TR) = 2000 ms; echo time (TE) = 30ms (3T)/ 40ms (1.5T); flip angle (FA) = 90°; field of view (FOV) = 22cm; voxel dimensions = 3.4375 × 3.4375 × 4 mm). One site (Duke/UNC) employed a spiral echo sequence, while all other sites used a single-shot EPI sequence. 140 volumes were collected in each run lasting 280s.

Functional volumes for both datasets were pre-processed using Statistical Parametric Mapping 8 (SPM8; Wellcome Trust Centre for Neuroimaging, UK). For each participant, each functional run was realigned, normalized to the Montreal Neurological Institute (MNI) EPI brain template (voxel size = 2 mm^3), and spatially smoothed with an 8mm full width at half maximum Gaussian filter. Following preprocessing, the SPM realignment parameters were examined, and any runs exceeding 3mm translation or 3° rotation were excluded from further analysis. This led to the removal of 29 runs in the fBIRN sample. Additional quality control procedures for the fBIRN sample included removing runs for images that showed artifacts and/or led to errors during preprocessing, and for runs in which there were few responses or a high false positive rate, suggesting participants were not engaged in the task. Further information on this quality control can be found in previous work (Lavigne, et al., 2016).

Data Analysis

Group fMRI-CPCA—fMRI data analysis was carried out using constrained principal component analysis for fMRI to compare groups (group fMRI-CPCA) with orthogonal rotation (Metzak, et al., 2011; Metzak, et al., 2012; Woodward, et al., 2006; Woodward, et al., 2013). The theory and proofs for CPCA are detailed in previously published work (Hunter and Takane, 2002; Takane and Hunter, 2001; Takane and Shibayama, 1991). The fMRI-CPCA application is available on-line, free of charge (www.nitrc.org/projects/fmricpca). fMRI-CPCA computes (via PCA) components representing functional brain networks on blood-oxygen level-dependent (BOLD) signal for which variance has been constrained (via multivariate multiple regression) to that predictable from task timing, and provides both spatial (dominant brain regions) and temporal (hemodynamic response shapes) information for each task-based functional brain network. When applied to multiple datasets, group fMRI-CPCA allows for visualization of task-common and task-specific networks, through observation of spatial and temporal replication across tasks within each network (Lavigne, et al., 2015a; Ribary, et al., 2017).

Group fMRI-CPCA involved the preparation of two matrices: (1) a data matrix (Z), containing the BOLD time series of each voxel, with one column per voxel and one row per whole brain scan; and (2) the design matrix (G), containing finite impulse response (FIR) models of the expected BOLD response to the timing onsets of stimulus presentations (i.e., pictures for the sentence task, target tones for the oddball task). In order to compare functional brain networks across experiments, data from all tasks (SP, VTG, AO) were included in Z, leading to a matrix of 115040 rows (158 subjects × up to 11 runs × up to 176

volumes) and 585,930 columns (voxels in $2mm^3$ resolution). Each column contained normalized and smoothed activations over all scans, with subjects, runs, and scans stacked vertically to produce *Z*. In *G*, a value 1 was placed in rows for which BOLD signal amplitude was to be estimated, and the value 0 in all other rows, creating "mini boxcar" functions. The columns of *G* code 7 poststimulus time points for each condition (SP, VTG, AO) for each of the (combined) 158 subjects, totaling 3318 columns ($7 \times 3 \times 158 = 3318$). These time points reflect different poststimulus time points in each study due to the difference in TR across studies, and are converted to seconds in the figures and results section to facilitate interpretation. Group fMRI-CPCA proceeds in two steps. First, the data matrix, *Z*, is regressed onto the design matrix, *G*, which partitions the overall variance into predicted and residual scores. The matrix predicted scores, which reflects variance in BOLD signal that is predictable from task timing, is then submitted to a principal component analysis (PCA), resulting in task-specific functional brain networks.

Relation to Experimental Conditions—Group fMRI-CPCA produces predictor weights for each combination of subject, task condition, and poststimulus time. These predictor weights, which provide estimates of the engagement of functional networks, can be analyzed statistically to determine whether or not they reflect reliable and biologically plausible HDR shapes, and whether differences between groups and/or task conditions exist within each network. These analyses were carried out for each task condition separately as three $3 \times 7 \times 3$ mixed-model ANOVAs (one each for SP, VTG, and AO), with the within-subjects factors of Component (3 components were extracted) and Poststimulus Time (7 whole brain scans after stimulus onset), and the between-subjects factor of Group (control, non-AVH, AVH). Significant three-way interactions were followed up with separate 7×3 ANOVAs for each component, and significant two-way interactions were followed up with simple contrasts comparing each Group pair at each level of Poststimulus Time. Tests of sphericity were carried out, and Greenhouse-Geisser adjustment in degrees of freedom for any analyses in which the assumption was violated did not affect interpretation of the results; therefore, the original degrees of free are reported below. Effect sizes (partial eta squared, η^2_p) are displayed.

Results

Group fMRI-CPCA

Inspection of the scree plot (Cattell, 1966; Cattell and Vogelmann, 1977) of singular values suggested three components should be extracted. The percentages of task-related variance accounted for by each component were 23.27%, 7.34%, and 4.60%, for Components 1 to 3, respectively. All components/tasks showed a significant effect of Poststimulus Time (all *p*s < .001; see Figures 2–4). Visual inspection of the predictor weights for each task condition confirmed a biologically plausible hemodynamic response shape for all components for SP and VTG task conditions, and for AO Component 1. Although AO Components 2 and 3 were reliable, they were not clearly valid with respect to a standard fMRI BOLD signal, opening the possibility that subtle but reliable coordinated (de)activations, uncorrected movement, or task-timing-predictable blood flow changes could contribute to this pattern.

Anatomical Descriptions—The cortical regions associated with Components 1 to 3 are displayed in Figure 5 A–C, with anatomical descriptions in Tables 2–4. Component 1 was characterized by activations in bilateral temporal pole (Brodmann Area (BA) 38), superior temporal gyrus (STG; BA 22), supplementary motor area (SMA; BA 6)/dorsal anterior cingulate cortex (dACC; BA 24), visual cortex (BA 17), left precentral gyrus (BA 6), bilateral insula, thalamus and cerebellum. This network included regions described as part of the auditory network described in Ćurčić-Blake *et al*'s review (2017) on AVHs in schizophrenia, as well as regions comprising the somatosensory network from Yeo and colleagues (Yeo, et al., 2011) resting-state fMRI parcellation analysis, and was labelled the *Auditory-Motor Network*. Component 2 was characterized by activations in left posterior middle temporal gyrus (BA 21), inferior frontal gyrus (IFG; BAs 44, 45), orbitofrontal cortex (BA 47), dorsolateral prefrontal cortex (BA 46), and bilateral visual cortex (BAs 17, 18, 19). These regions correspond to Broca's and Wernicke's areas, as well as other regions involved in language processing, and are similar to the language network described in previous research (Ćurčić-Blake, et al., 2017); this network was, therefore, called the *Language Processing Network*. Component 3 was characterized by activations in bilateral superior temporal gyrus (BA 22), visual cortex (BAs 18, 19), left precentral gyrus/SMA (BAs 4, 6) and primary auditory cortex (BA 41), and deactivations in bilateral ventromedial prefrontal cortex (BAs 9, 10, 11), precuneus (BAs 5, 7), posterior cingulate cortex (BA 30), and lateral occipital cortex (BAs 39/40), regions comprising the *Default-Mode Network* (DMN; Buckner, et al., 2008; Raichle and MacLeod, 2001).

Relations to Experimental Conditions—The three-way interactions were not significant for SP or VTG (*p*s > .63). Therefore, for verbal conditions, the components were combined, and 7 (Poststimulus Time) × 3 (Group) ANOVAs were computed for each task condition separately. For SP (Figure 2), there was a significant Poststimulus Time × Group interaction, $F(12,282) = 2.72$, $p < .05$, $\eta^2_p = .10$, and a main effect of Group, $F(2,47) = 7.83$, $p < .005$, $\eta^2_p = .25$. The Poststimulus Time × Group interaction was interpreted by investigating simple main effects of Group at each time point. This showed significantly increased activity in (1) AVH patients relative to controls at 3.75s, 6.25s, and 8.75s; (2) AVH relative to non-AVH patients at 6.25s and 8.75s; and (3) non-AVH relative to both controls and AVH patients at 13.75s. For VTG (Figure 3), a significant Poststimulus Time × Group interaction, $F(12,282) = 2.94$, $p < .05$, $\eta^2_p = .11$, and a significant main effect of Group, $F(2,47) = 3.43$ $p < .05$, $\eta^2_p = .13$, were observed. Simple contrasts of Group at each time point revealed that this interaction was due to increased activity in AVH patients relative to controls at 6.25s and 8.75s. Although no significant differences emerged between AVH and non-AVH patients, nor between controls and non-AVH patients on VTG, activity in the non-AVH group was situated midway between controls and AVH patients at peak, which also contributed to the significant interaction effect.

For AO (Figure 4), there was a significant Component × Poststimulus Time × Group interaction, $F(24,1260) = 3.36$, $p < .001$, $\eta^2_p = .06$. This was followed up by three 7 (Poststimulus Time) × 3 (Group) ANOVAs, one for each component. All three networks showed a significant interaction between Poststimulus Time and Group, $F(12,630) = 3.77$, $p < .005$, $\eta^2_p = .07$, $F(12,630) = 2.22$, $p < .05$, $\eta^2_p = .04$, and $F(12,630) = 3.98$, $p < .005$, η^2_p

= .07, for Components 1-3, respectively. This was interpreted using simple contrasts. For the Auditory-Motor network (Component 1), this revealed increased activity in controls relative to both non-AVH, at 7s, and AVH patients at 5s and 7s. For the Language Processing Network (Component 2), controls showed greater activity than both patient groups at 7s and 9s. In contrast, controls showed *decreased* intensity (i.e., both lesser activations and deactivations) relative to non-AVH patients at 7s, 9s, and 11s and AVH patients at 7s and 9s on the DMN (Component 3). There were no significant differences between the patient groups on any of the three components.

Discussion

In the current study, we investigated whether hypercoupling in speech-related brain networks in schizophrenia patients with AVHs is specific to verbal material by combining previously-published data from verbal (SP, VTG) and non-verbal (AO) auditory fMRI datasets in schizophrenia patients with and without AVHs and healthy controls. Using a statistical analysis technique allowing for comparison of coordinated activity in task-related brain networks across groups and tasks while holding the network under study constant, we identified separate auditory-motor, language processing, and default-mode networks. During SP, AVH patients showed hypercoupling across all networks relative to the other groups; during VTG, AVH patients showed hypercoupling relative to controls, but did not differ from non-AVH patients, replicating our previous study (Lavigne, et al., 2015b). Finally, diagnosis-rather than symptom-specific differences were observed for all three components during AO, suggesting that hypercoupling in speech-related brain networks (and the DMN) in AVH patients is specific to verbal perceived stimuli. These findings are consistent with symptom capture and resting state studies pointing to hyperactivity in speech and auditory networks as an important factor in the generation of AVHs in schizophrenia (Ćurčić-Blake, et al., 2017), and support the notion that this hypercoupling is a core feature of AVHs in schizophrenia, and is not present when control is exerted over verbal material, such as during inner speech.

By combining data from separate studies, and using group fMRI-CPCA to extract common networks, we were able to identify common and distinct functional brain networks elicited by each experiment. Much like including multiple conditions in a single study, this method provides a means of comparing network-level HDR shapes for different tasks on the same networks, overcoming the confounding factor of comparing different brain networks across tasks (Lavigne, et al., 2015a; Ribary, et al., 2017). Thus, the auditory-motor network showed strong coordinated activations for SP and AO, both of which involved auditory stimuli, but not for VTG, for which sentences were internally generated. In contrast, the language processing network showed strong coordinated activations for the verbal tasks (VTG and SP), but not for the non-verbal AO task. Importantly, combining the AO and sentence tasks allowed the auditory-motor and language networks to separately emerge, whereas they were aggregated onto one network in our previous sentence task study (Lavigne, et al., 2015b). These differential patterns of coordinated activity across tasks, along with the networks' spatial configurations, allow us to interpret the function of these networks with increased accuracy, and provide a more fine-grained understanding of the networks (and subnetworks) underlying AVHs in schizophrenia.

Auditory Oddball (AO)

Although the auditory-motor network showed the greatest degree of activity during AO, AO showed no differences between the hallucination-based patient groups on this (or the other two) networks. These findings provide evidence that the hypercoupling in speech-related brain networks observed in SP is not present during presentation of non-verbal auditory stimuli in schizophrenia patients with AVHs. Instead, patients showed hypoactivity, or reduced coupling, in this network regardless of hallucination status during oddball processing, which is in line with previous research on auditory oddball processing in schizophrenia (Kim, 2014; Wynn, et al., 2015), and is also consistent with our previously published study (Lavigne, et al., 2016). Moreover, in addition to auditory-motor regions, this network included nodes of the ventral attention network (i.e., bilateral insula and anterior cingulate cortex), which has been strongly implicated in auditory oddball deficits in schizophrenia (Kim, 2014).

AO produced a reliable but not clearly biologically plausible HDR shape on the language processing network, suggesting that, as expected given the non-verbal nature of the task, this task does not elicit standard linguistic processes. This supports our selection of AO as a suitable comparison task condition for the current study. In fact, AO showed evidence of deactivity on this network during target detection, a finding suggesting suppression of language regions (relative to baseline) during non-verbal auditory processing. Despite the reduced activation observed on this network in AO relative to the other tasks, we were still able to detect group differences. As with the auditory-motor network, these were diagnosis- rather than symptom-based, and showed a similar pattern of decreased activity in patients relative to controls, with no differences between hallucination-based patient groups.

Verbal Thought Generation (VTG)

No significant differences between hallucination-based groups were observed during VTG. Although AVH patients demonstrated increased activity in all three networks relative to controls, this activity did not differ from that of non-AVH patients, which, in turn, did not differ from controls. These findings differ slightly from our previous study, in which both patient groups showed significantly greater activation than controls on VTG, and was interpreted as reflecting top-down processes in terms of expectation of control over verbal material. Although the sentence task samples were identical between the two studies, these between-study differences could be explained by the novel networks that emerged from the new analysis, and/or the reduced cut-off for hallucination severity used in order to equate the groups across studies, which may have obscured the previously reported effect in the current study. However, this absence of difference between groups should be interpreted with caution, as they may become significant with increased power.

Default-mode Network (DMN)

The finding of STG activations coordinating with DMN deactivations on Component 3 (dominated by SP) is likely due to STG peaking at both 6.25 and 8.75s on Component 3 (and at 8.75s on Component 1). Component 3 demonstrates that the STG 6.25/8.75s peaks increase simultaneously with the DMN decreases, but this does not imply that they are causally related, which cannot be determined with functional connectivity analysis methods.

Thus, we interpret Component 3 as being driven primarily by DMN deactivations, but also coordinating activation in task-positive regions occurring at 6.25/8.75s (with the 8.75s STG peak captured on Component 1).

As was the case with the other two networks, only diagnosis-based differences emerged on the DMN for AO and VTG, with differences emerging between the AVH and non-AVH groups during SP. The DMN is commonly associated with self-referential processing and recollection of autobiographical memories (Buckner, et al., 2008), but also shows increased deactivation during reality monitoring, which involves distinguishing between information that is self- or other-generated (Metzak, et al., 2015). Since the DMN consists of negative loadings, increased deactivations can also be interpreted as decreased activations for the DMN; therefore, decreased coordinated activation for the DMN network in hallucinations may contribute to a loss of self-source tags (alienation) for verbal material, leading to inner, verbal thought generated events being experienced as not inner or not self-generated, or as neither (Larøi and Woodward, 2007; Woodward and Menon, 2013), contributing to the formation of hallucinations. This interpretation is in line with previous findings reported an anticorrelation between the DMN and AVH-related regions during the resting state (Alderson-Day, et al., 2016; Jardri, et al., 2012).

Other Literature

Using a larger sample of the fBIRN AO dataset, Ford and colleagues (2009) reported hypoactivity in left primary auditory cortex in AVH relative to non-AVH patients, interpreting this as oddball tones competing for neural resources with voices. Although these findings appear to contradict the current results, it is difficult to directly compare them due to differences in the subsamples used, as well as the use of different analysis techniques. Particularly, our use of a network-based connectivity method may not detect a region-specific effect, although a region-specific effect should still emerge on a distinct network. Research using other non-verbal auditory tasks has also reported differences between hallucinating and non-hallucinating patients, for example, in pitch discrimination and melodic streaming (McLachlan, et al., 2013) and spoken non-verbal sounds (Rossell and Boundy, 2005). There is also evidence that auditory imagery recruits similar regions to AVHs, with one study finding that the timing of activation in the SMA distinguished between the two conditions (Linden, et al., 2010). Our VTG condition shows similarities to auditory imagery; however, due to the network-based nature of the analysis, we were not able to distinguish between timing of activation in the SMA and auditory regions, as these emerged on the same network. From the current findings, we can conclude that the networks showing hypercoupling in AVH patients during SP do not show the same pattern during the presentation of non-verbal auditory oddball stimuli. Future research will be necessary to tease apart these seemingly contradictory findings.

Although there is robust evidence that auditory and language networks are more active during hallucination-on than hallucination-off periods (Jardri, et al., 2011), the trait-based literature is more equivocal. For example, a meta-analysis comparing brain activations during the experience of hallucinations versus external auditory stimuli in AVH patients suggested that external sounds led to hypoactivation in auditory and language regions;

however, several of these studies included non-verbal auditory stimuli. One possibility for these equivocal findings concerns the lack of reporting whether AVHs occurred during the scanning session in trait-based studies. Hyperactivity to external (verbal) stimuli may occur in the absence of AVHs, and hypoactivity in the presence of AVHs, but it is not possible to determine this without knowledge of whether participants were hallucinating during the session. Another interpretation is that an optimal level of connectivity is required, such that either hyperactivity or hypoactivity results in AVHs (Ćurčić-Blake, et al., 2017). Finally, differences in experimental design, analysis methodology (especially network versus ROI-based studies), and clinical status of patients (phenomenology of hallucinations, course of illness, etc) may also contribute to these equivocal findings.

Limitations

One limitation of this study is that the verbal and non-verbal tasks used independent samples and study sites, leading to the possibility that site differences contributed to our interpretation of some of the results. This also prevented us from directly comparing the conditions statistically; therefore, our comparisons of significant to non-significant results across tests should be explicitly tested in future research with a within-subjects design. Although neuroimaging research is increasingly combining data from separate studies, a within-subjects design including experimentally-controlled verbal and non-verbal auditory tasks would be more definitive. Another disadvantage of combining separate studies is the use of different assessment measures, which was the case in the current study for symptoms, though we attempted to equate the AVH group across tasks as closely as possible by including patients endorsing any degree of auditory hallucinations in the AVH groups. Moreover, although all patients who completed the sentence task were confirmed to be experiencing auditory verbal hallucinations in the past week, this could not be definitively confirmed for eight fBIRN subjects due to the nature of using publicly available data. Future research examining the phenomenology of hallucinations in more depth would speak to the generalizability of these findings. Finally, the auditory oddball paradigm involves cognitive processes in addition to perception of non-verbal auditory stimuli (e.g., monitoring, vigilance), and is more commonly used in research on attention and salience detection, and not often in the context of AVHs. While a non-verbal auditory task with certain perceptual qualities matched to verbal material would be better suited to address our research question, the current secondary analysis leverages immediately available, publicly available resources to provide strong preliminary support for the notion that hypercoupling in speech-related brain networks is specific to verbal material.

Conclusion

The current findings provide evidence that hypercoupling in speech-specific brain networks in schizophrenia patients with hallucinations is specific to verbal material, an underlying assumption of several theories of AVHs in schizophrenia. It also confirmed previous research (Lavigne, et al., 2015b) suggesting that, for schizophrenia patients with hallucinations, the expectation of exerting cognitive control attenuated both increased activation of networks involving temporal-frontal regions and increased reduction of DMN. From this, we can speculate that, clinically, expecting to control inner verbal thought processes may reduce hypercoupling in speech-related functional networks and reduce the

likelihood of hallucinations. However, future research should attempt to replicate these findings using a within-subjects design with a dedicated non-verbal auditory condition, in order to determine whether this hypercoupling is a core feature of AVHs in schizophrenia.

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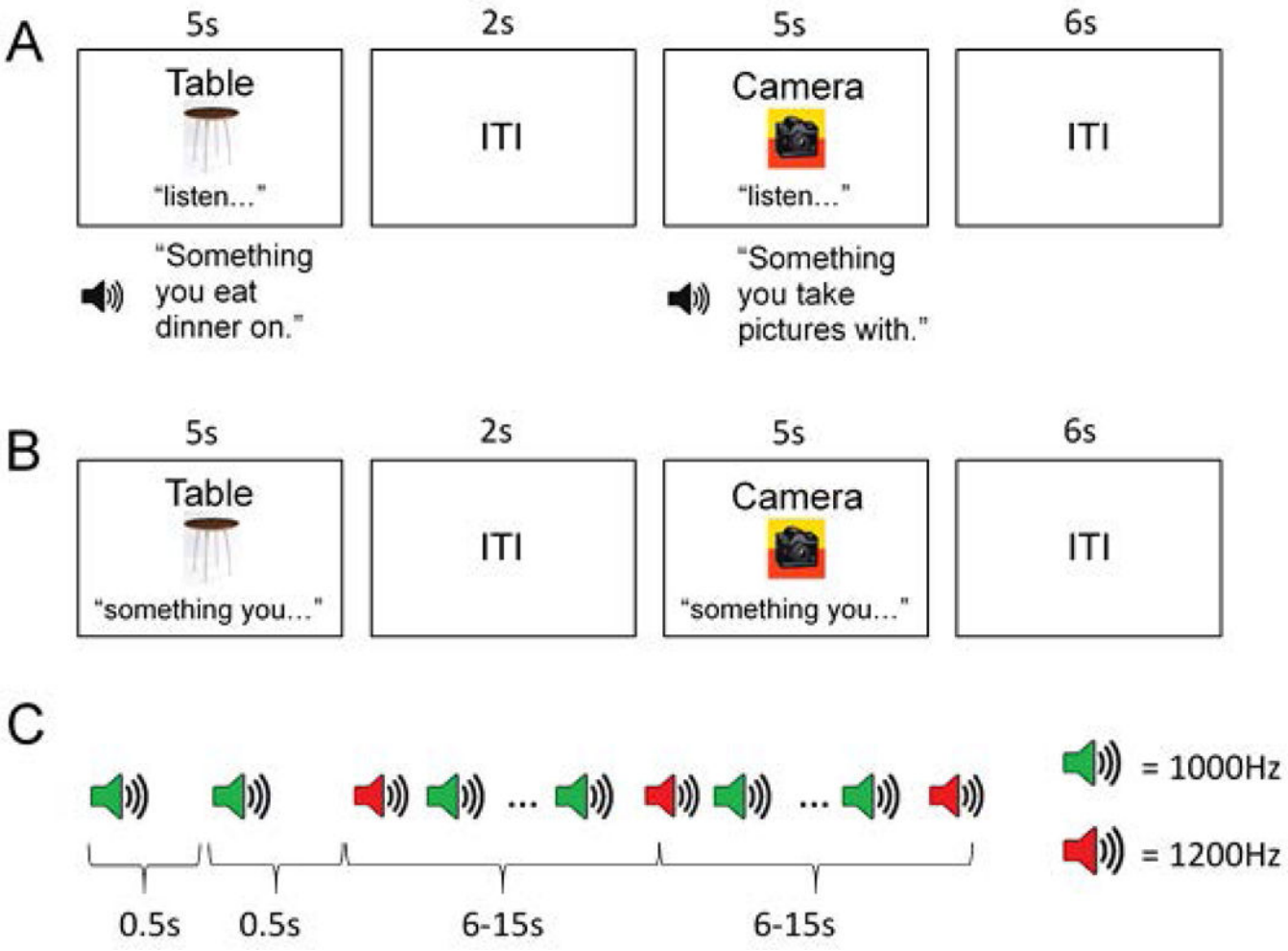

Figure 1.
Timelines of the experimental paradigms. A: Speech Perception (SP). B: Verbal Thought Generation (VTG). C: Auditory Oddball (AO).

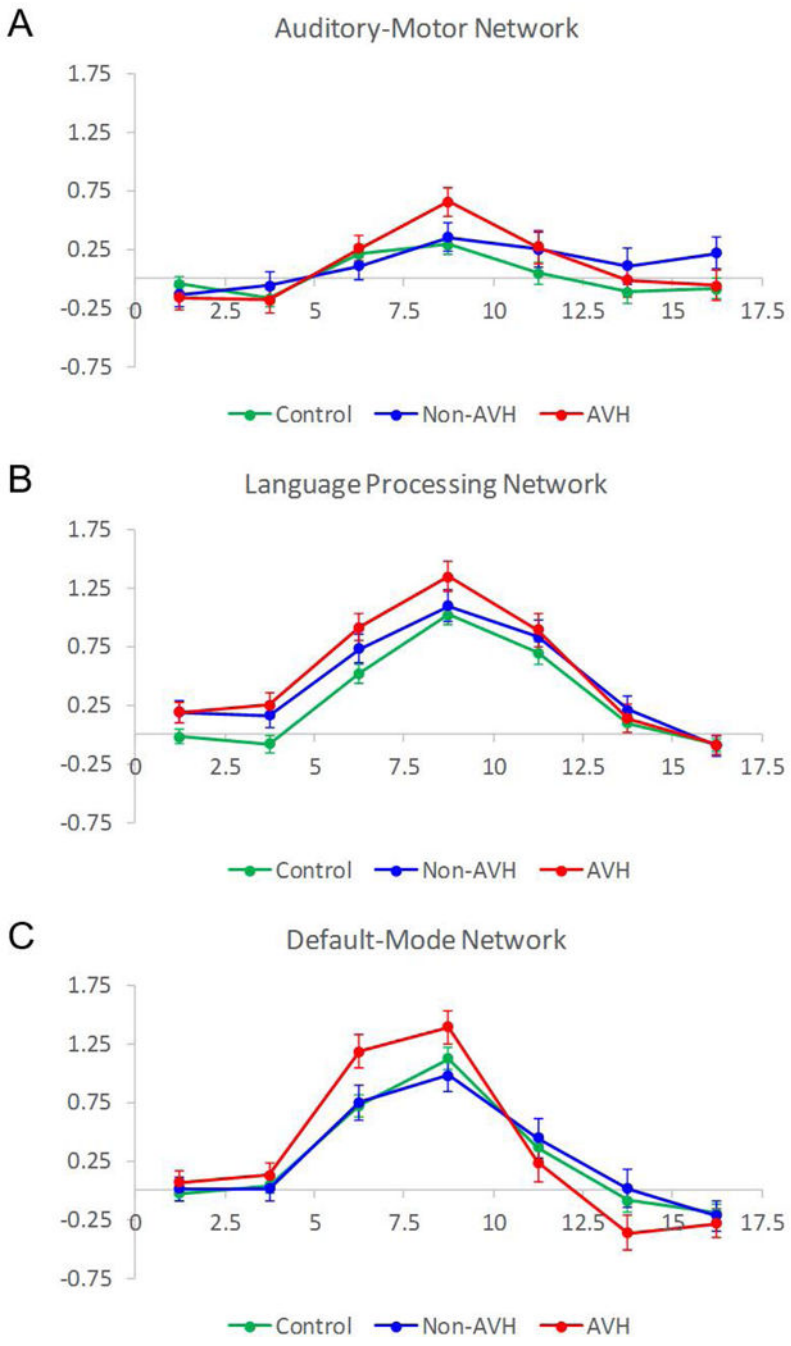

Figure 2.

Mean finite impulse response (FIR)-based predictor weights for Speech Perception (SP) plotted as a function of poststimulus time. A: Auditory-Motor Network. B: Language Processing Network. C: Default-Mode Network. AVH = auditory-verbal hallucinations.

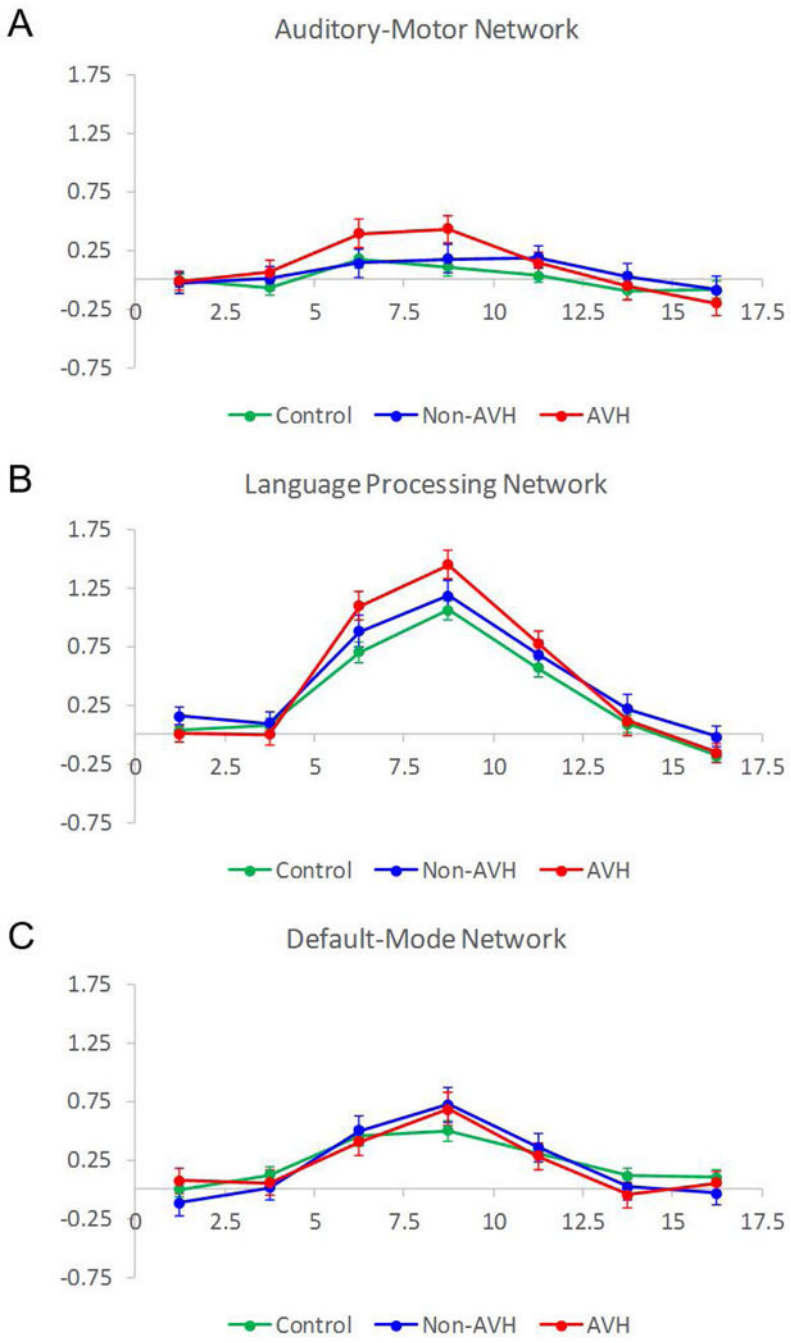

Figure 3.

Mean finite impulse response (FIR)-based predictor weights for Verbal Thought Generation (VTG) plotted as a function of poststimulus time. A: Auditory-Motor Network. B: Language Processing Network. C: Default-Mode Network. AVH = auditory-verbal hallucinations.

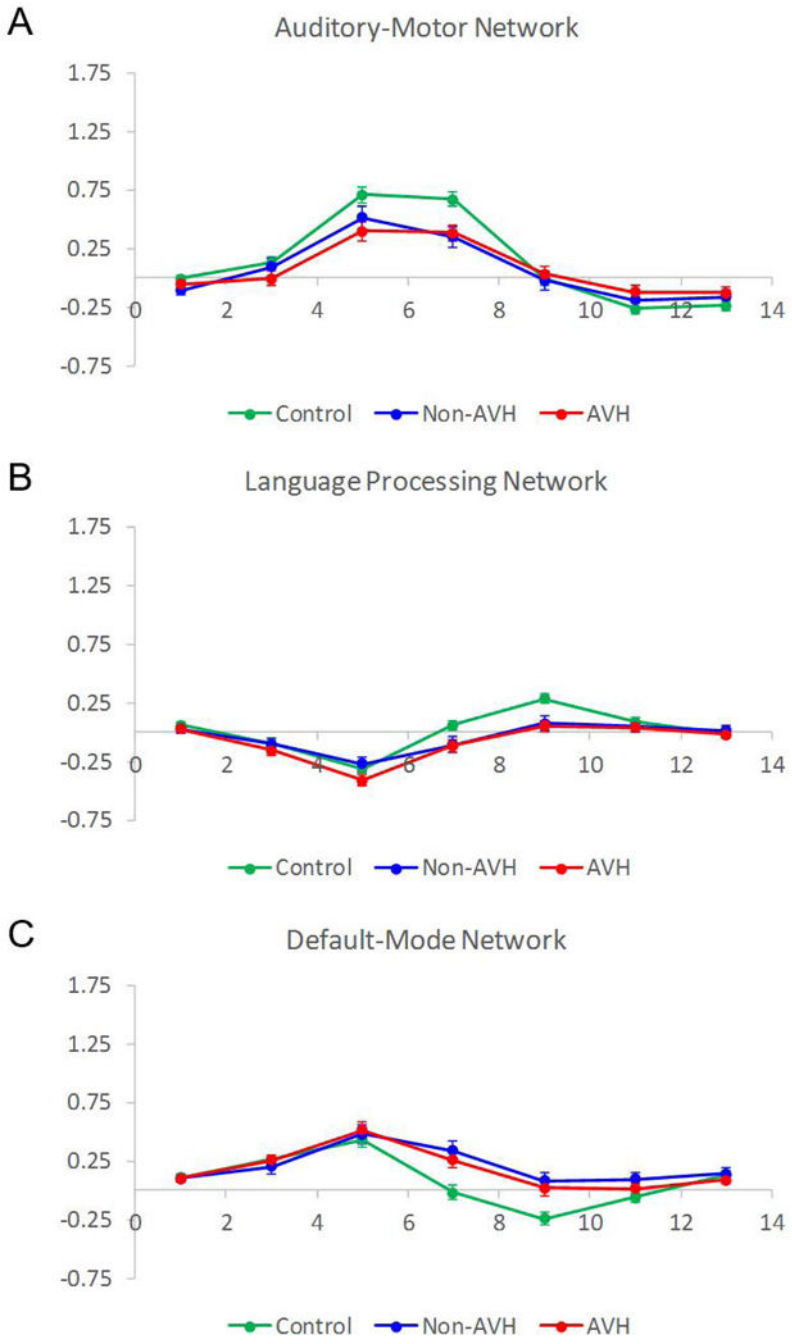

Figure 4.

Mean finite impulse response (FIR)-based predictor weights for Auditory Oddball (AO) plotted as a function of poststimulus time. A: Auditory-Motor Network. B: Language Processing Network. C: Default-Mode Network. AVH = auditory-verbal hallucinations.

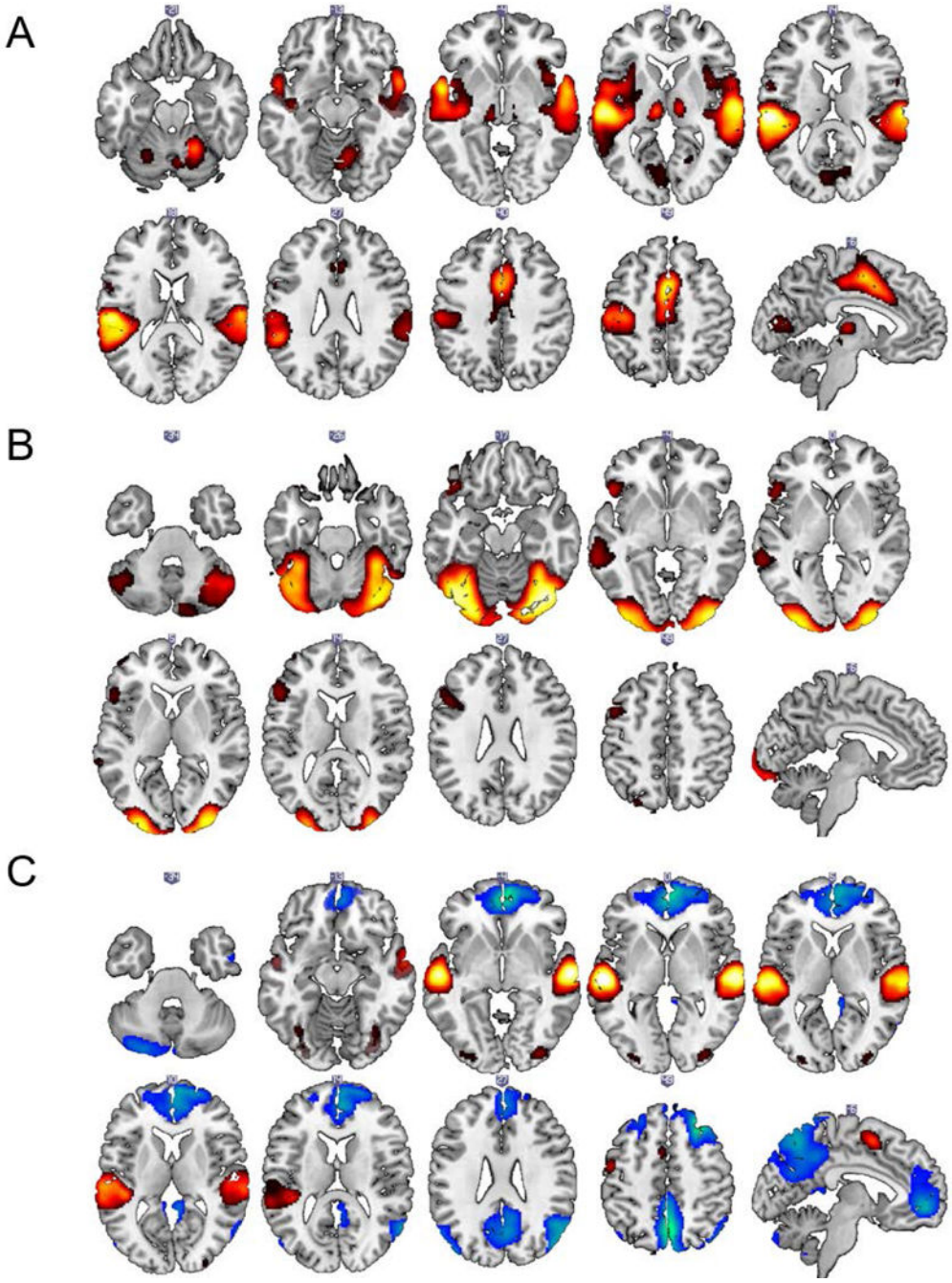

Figure 5.

Dominant 10% of component loadings for A: Auditory-Motor Network (Component 1, red/yellow = positive loadings, threshold = 0.11, max = 0.18; no negative loadings passed threshold), B: Language Processing Network (Component 2, red/yellow = positive loadings, threshold = 0.07, max = 0.15; blue/green = negative loadings, threshold = −0.07, min = −0.07), and C: Default-Mode Network (Component 3, red/yellow = positive loadings,

threshold = 0.05, max = 0.11; blue/green = negative loadings, threshold = −0.05, min = −0.09). Montreal Neurological Institute Z-axis coordinates are displayed.

Table 1

Demographic information for each group and study.

	Sentence Task			Auditory Oddball		
	Control	**Non-AVH**	**AVH**	**Control**	**Non-AVH**	**AVH**
Demographics						
N	27	11	12	50	23	35
Gender (male:female)	16:11	6:5	6:6	34:16	15:8	30:5
Handedness	25:2	10:1	12	48:2	21:2	32:3
Age	28.89 (8.98)	35.45 (8.96)	30.08 (9.72)	34.88 (12.82)	40.61 (13.43)	35.57 (11.93)
Hallucinations Type						
Auditory-Verbal	**–**	**–**	**12**	**–**	**–**	**35**
Somatic-Tactile	**–**	**–**	**6**	**–**	**–**	**10**
Olfactory	**–**	**–**	**1**	**–**	**–**	**6**
Visual	**–**	**–**	**3**	**–**	**–**	**13**

Note. AVH = Auditory verbal hallucinations.

Table 2

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

Brain Regions	Cluster Volume (voxels)	BAs for Peak Locations	MNI Coordinate for Peak Locations		
			x	y	z
Positive Loadings					
Cluster 1: Left Hemisphere	11850				
Planum temporale		22	−60	−24	10
Precentral gyrus		4	−40	−20	60
Planum polare		38	−56	2	−4
Insular cortex		48	−36	−22	2
Precentral gyrus		6	−58	4	16
Cluster 2: Right Hemisphere	7100				
Planum temporale		22	62	−18	6
Superior temporal gyrus, anterior division		21	58	0	−6
Temporal pole		38	56	6	−8
Insular cortex		48	40	10	0
Planum polare		48	40	−8	−14
Cluster 3: Bilateral	3854				
Supplementary motor area/Dorsal anterior cingulate cortex		6/24	−2	4	46
Cluster 4: Right Hemisphere	1483				
Cerebellum VI		n/a	20	−54	−22
Cerebellum V		n/a	8	−62	−14
Cluster 5: Bilateral	1113				
Intracalcarine cortex		17	−6	−78	10
Intracalcarine cortex		17	14	−72	12
Cluster 6: Left Hemisphere	485				
Thalamus		n/a	−10	−18	6
Cluster 7: Left Hemisphere	341				
Cerebellum VI		n/a	−24	−60	−24
Cluster 8: Right Hemisphere	324				
Thalamus		n/a	12	−16	6
Cluster 9: Right Hemisphere	14				
Supramarginal gyrus, anterior division		40	52	−34	54
Cluster 10: Right Hemisphere	12				
Middle frontal gyrus		6	42	0	58
Negative Loadings: No negative loadings passed threshold.					

Table 3

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

Brain Regions	Cluster Volume (voxels)	BAs for Peak Locations	MNI Coordinate for Peak Locations		
			x	y	z
Positive Loadings					
Cluster 1: Bilateral	21500				
Occipital fusiform gyrus		19	40	−72	−18
Occipital fusiform gyrus		19	−44	−66	−20
Lateral occipital cortex, inferior division		19	−42	−76	−16
Lateral occipital cortex, inferior division		18	40	−90	−8
Occipital fusiform gyrus		18	−28	−84	−20
Occipital pole		18	−28	−98	6
Occipital pole		18	32	−94	8
Occipital pole		17	16	−104	4
Lingual gyrus		18	−4	−90	−16
Occipital pole		17	−4	−102	−12
Cerebellum crus II		n/a	26	−76	−48
Temporal fusiform cortex		20	34	−24	−32
Cluster 2: Left Hemisphere	3646				
Frontal orbital cortex		45	−48	24	−6
Inferior frontal gyrus, pars triangularis		45	−52	22	16
Frontal pole		11	−28	64	−16
Middle frontal gyrus		6	−48	6	48
Frontal pole		46	−42	56	10
Inferior frontal gyrus, pars opercularis		44	−38	8	30
Middle frontal gyrus		44	−50	16	36
Cluster 3: Left Hemisphere	1029				
Middle temporal gyrus, posterior division		21	−64	−38	−2
Cluster 4: Right Hemisphere	201				
Frontal pole		47	30	66	−18
Cluster 5: Left Hemisphere	117				
Lateral occipital cortex, superior division		7	−28	−76	48
Cluster 6: Left Hemisphere	17				
Superior frontal gyrus		6	−4	18	70
Cluster 7: Left Hemispere	16				
Superior frontal gyrus		6	−4	18	56
Cluster 8: Left Hemisphere	15				
Hippocampus		20	−20	−32	−6
Negative Loadings					
Cluster 1: Right Hemisphere	22				

Brain Regions	Cluster Volume (voxels)	BAs for Peak Locations	MNI Coordinate for Peak Locations		
			x	y	z
Supramarginal gyrus, anterior division		48	60	−24	24

Table 4

Cluster volumes for the most extreme 10% of Default-Mode Network (Component 3) loadings, with anatomical descriptions, Montreal Neurological Institute (MNI) coordinates, and Brodmann's area (BA) for peaks within each cluster.

Brain Regions	Cluster Volume (voxels)	BAs for Peak Locations	MNI Coordinate for Peak Locations		
			x	y	z
Positive Loadings					
Cluster 1: Left Hemisphere	2457				
Superior temporal gyrus, posterior division		22	−58	−18	0
Planum temporale		41	−50	−40	20
Cluster 2: Right Hemisphere	2154				
Superior temporal gyrus, posterior division		22	62	−16	−2
Cluster 3: Bilateral	405				
Supplementary motor area		6	−4	4	56
Cluster 4: Right Hemisphere	220				
Lateral occipital cortex, inferior division		19	32	−88	−4
Occipital fusiform gyrus		19	34	−72	−12
Cluster 5: Left Hemisphere	91				
Precentral gyrus		6	−52	−6	48
Cluster 6: Right Hemisphere	66				
Temporal occipital fusiform cortex		37	34	−50	−22
Cluster 7: Left Hemisphere	58				
Precentral gyrus		4	−38	−24	56
Cluster 8: Left Hemisphere	28				
Occipital pole		18	−26	−90	−8
Cluster 9: Left Hemisphere	14				
Occipital fusiform gyrus		19	−36	−66	−14
Negative Loadings					
Cluster 1: Bilateral	10692				
Precuneus cortex		7	2	−62	48
Lateral occipital cortex, superior division		39	44	−76	38
Lateral occipital cortex, superior division		7	8	−64	68
Precuneus cortex		5	−6	−54	72
Cuneal cortex		19	4	−92	44
Cingulate cortex, posterior division		30	4	−46	8
Precuneus cortex		5	6	−46	76
Superior parietal lobule		7	24	−54	72
Lateral occipital cortex, superior division		19	22	−86	48
Angular gyrus		40	46	−50	60
Occipital pole		18	2	−102	26
Cluster 2: Bilateral	7221				
Middle frontal gyrus		9	28	32	48

Brain Regions	Cluster Volume (voxels)	BAs for Peak Locations	MNI Coordinate for Peak Locations		
			x	y	z
Frontal pole		10	6	58	−4
Paracingulate gyrus		32	4	50	12
Frontal pole		9	6	50	46
Frontal pole		8	6	42	54
Frontal pole		10	−22	58	8
Superior frontal gyrus		8	6	32	60
Frontal pole		11	−24	56	0
Cluster 3: Left Hemisphere	1584				
Lateral occipital cortex, superior division		19	−42	−84	32
Lateral occipital cortex, superior division		39	−50	−78	26
Cluster 4: Bilateral	1172				
Cerebellum crus I		n/a	−36	−78	−38
Cerebellum crus II		n/a	−46	−64	−46
Cluster 5: Left Hemisphere	345				
Frontal pole		9	−26	38	42
Cluster 6: Right Hemisphere	35				
Cerebellum crus II		n/a	44	−66	−48
Cluster 7: Left Hemisphere	11				
Lateral occipital cortex, inferior division		37	−64	−66	−6