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Hypoactivation of the language network during auditory imagery contributes to hallucinations in Schizophrenia

Luca Besso [a,b], Sara Larivière [c], Meighen Roes [a,d], Nicole Sanford [b], Chantal Percival [a,b,e], Matteo Damascelli [f], Ava Momeni [a,b], Katie Lavigne [g,h], Mahesh Menon [b], André Aleman [i], Branislava Ćurčić-Blake [i], Todd S. Woodward [a,b,*]

[a] BC Mental Health and Addictions Research Institute, Provincial Health Services Authority, Vancouver, BC, Canada
[b] Department of Psychiatry, University of British Columbia, Vancouver, BC, Canada
[c] Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA
[d] Department of Psychology, University of British Columbia, Vancouver, BC, Canada
[e] Faculty of Medicine, University of British Columbia, Vancouver, BC, Canada
[f] School of Population and Public Health, Faculty of Medicine, University of British Columbia, Vancouver, BC, Canada
[g] Douglas Research Centre, Montreal, Quebec, Canada
[h] Department of Psychiatry, McGill University, Montreal, Quebec, Canada
[i] Department of Biomedical Sciences of Cells and Systems, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands

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ABSTRACT

Auditory verbal hallucinations (AVHs) involve perceptions, often voices, in the absence of external stimuli, and rank among the most common symptoms of schizophrenia. Metrical stress evaluation requires determination of the stronger syllable in words, and therefore requires auditory imagery, of interest for investigation of hallucinations in schizophrenia. The current functional magnetic resonance imaging study provides an updated whole-brain network analysis of a previously published study on metrical stress, which showed reduced directed connections between Broca's and Wernicke's regions of interest (ROIs) for hallucinations. Three functional brain networks were extracted, with the language network (LN) showing an earlier and shallower blood-oxygen-level dependent (BOLD) response for hallucinating patients, in the auditory imagery condition only (the reduced activation for hallucinations observed in the original ROI-based results were not specific to the imagery condition). This suggests that hypoactivation of the LN during internal auditory imagery may contribute to the propensity to hallucinate. This accords with cognitive accounts holding that an impaired balance between internal and external linguistic processes (underactivity in networks involved in internal auditory imagery and overactivity in networks involved in speech perception) contributes to our understanding of the biological underpinnings of hallucinations.

1. Introduction

Auditory verbal hallucinations (AVHs) involve perceptions, often of voices, in the absence of external stimuli. Approximately 75 % of patients with schizophrenia experience AVHs at some point in the course of their illness, making it one of the most common symptoms of schizophrenia (Allen et al., 2008; McGuire et al., 1993; Thomas et al., 2007). Evaluation of metrical stress is a cognitive task that invokes auditory imagery (imagery of speech sounds) by requiring determination of the 'stressed' syllable in bisyllabic words (Aleman et al., 2005). This paradigm has been used for neuroimaging studies of AVHs because auditory imagery may invoke cognitive processes that are relevant to hallucinations, such as source misidentification involving internally-generated thoughts attributed to an external source (Allen et al., 2008; Bentall, 1990a; Frith and Done, 1988; Larøi and Woodward, 2007; Woodward and Menon, 2013).

A previous functional magnetic resonance imaging (fMRI) study using the metrical stress task in the context of AVHs was conducted by B. Ćurčić-Blake et al. (2013). In their study, they investigated the hypothesis that AVHs are a result of dysfunctional interhemispheric and

* Correspondence to: Room A3-A117, BC Mental Health & Addictions Research Institute – Translational Research Building, 3rd Floor, 938W. 28th Avenue, Vancouver, British Columbia V5Z 4H4, Canada.
E-mail address: Todd.S.Woodward@gmail.com (T.S. Woodward).

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frontotemporal connectivity between Broca's and Wernicke's areas. The results suggested that hallucinating patients show reduced connectivity between Broca's and Wernicke's area, and it was concluded that reduced input to Broca's area causes activity in this region to become less constrained by perceptual input (Aleman and Larøi, 2008; Behrendt, 2003; Grossberg, 2000).

The previous analyses were based on the *a priori* selection of regions of interest (ROIs). Although this is typical of many fMRI studies (Poldrack, 2007; Stephan et al., 2010), it is well accepted that the brain functions in terms of networks (Li et al., 2009; Medaglia et al., 2015), and focussing solely on a restricted number of ROIs cannot allow the study of naturally occurring macro-scale whole-brain networks. Expansion of these ROI-based studies to whole-brain networks is becoming increasingly common, and has provided novel insights into the neural underpinnings of psychiatric disorders (Goghari et al., 2017; Lavigne, Rapin, et al., 2015; Williamson and Allman, 2012; Woodward et al., 2015).

The study of whole-brain BOLD networks with task-based fMRI isrelatively rare. Far more common is a univariate approach involving a univariate application of statistical parametric mapping (SPM) using the standard general linear model (GLM) on a voxel-by-voxel basis (Friston, 2007). The application of the SPM/GLM procedure precludes observation of naturally occurring macro-scale brain networks, not only because it is a univariate application, but also because it typically restricts interpreted results to task-induced blood-oxygen-level-dependent (BOLD) signal changes that match an assumed model (Josephs et al., 1997). Restricting results to assumed models neglects the rich spatial and temporal information that is readily observable through study of naturally occurring BOLD networks and their task-induced BOLD signal fluctuations. Moreover, this spatial and temporal information can be interpreted to determine the distinct cognitive functions associated with each network (Lavigne, Metzak, et al., 2015; Metzak et al., 2012; Wong et al., 2020).

Previous cognitive accounts suggest that AVHs arise from an imbalance between internal and external sources in source monitoring, with the balance shifted away from internal processing and towards external processing (Larøi and Woodward, 2007; Woodward and Menon, 2013). Internal versus external processing of linguistic stimuli maps onto the whole-brain network imaging literature, with internal processing eliciting a Broca's and Wernicke's area-based language network (LN; Lipkin et al., 2022; Fedorenko et al., 2024), and external language perception activating superior temporal gyrus-based network (STG; Belin et al., 2000; Binder et al., 2000).

Reviews of the fMRI/hallucinations literature (Curcic-Blake et al., 2017) have focussed on both the LN and STG, with hyperactivity typically reported (Allen et al., 2008, 2012; Lavigne et al., 2015; Lavigne and Woodward, 2018; Homan et al., 2013; Alonso-Solís et al., 2015; Rolland et al., 2015; Lavigne and Woodward, 2018; Lavigne et al., 2015). However, the LN is not normally separated from the STG network in most studies, but they are listed alongside one another, typically as hyperactive in hallucinations (Allen et al., 2008, 2012; Ćurčić-Blake et al., 2013; Jardri et al., 2011). The LN/STG distinction is important, because it can be mapped roughly onto 'internal'/'external' linguistic processing, respectively, and in this way is pertinent to cognitive accounts suggest that AVHs arise from an imbalance between internal and external sources in source monitoring, with the balance is shifted away from internal processing towards external processing (Larøi and Woodward, 2007; Woodward and Menon, 2013). The LN/STG distinction should therefore be separated in brain imaging research on hallucinations in order to provide a way to link the 'internal/external' cognitive account of hallucinations with brain imaging results; however, the STG does not emerge with tasks not involving auditory perception (Sanford et al., 2020, Figure S3).

Here, we provide an update on the previous analysis of Ćurčić-Blake et al. (2013) using a network-level task-based approached called group-constrained principal component analysis for fMRI (group fMRI-CPCA; Metzak et al., 2011; Woodward et al., 2015; www.nitrc.org/projects/fmricpca). Our approach uses a finite impulse response (FIR) model to constrain the variance in the BOLD signal fluctuations to that predictable by task timing, and PCA is applied to the variance-constrained BOLD signal to observe macro-scale whole-brain networks and their task-induced BOLD changes, with the latter being compared between groups. The FIR model identifies the task-induced BOLD signal changes that appear consistently over stimulus presentation trials, making no *a priori* assumptions regarding hemodynamic response (HDR) shapes, allowing observation of the unique HDR curves separate networks can simultaneously produce. We expected multiple task-based brain networks to emerge, but with the hallucination-specific reduction in coordinated activity observed in past work (Ćurčić-Blake et al., 2013) to be restricted to the LN.

2. Methods

2.1. Participants

Forty-seven schizophrenia patients with a diagnosis confirmed by the Schedules for Clinical Assessment in Neuropsychiatry (SCAN 2.1) interview (Health, 1994) were included. Patients were classified into currently (past week) non-hallucinating (NoAVH group; $n = 26$), and currently (past week) hallucinating (AVH group; $n = 21$) patients by a score of 5 (moderate severe) or higher on the Positive and Negative Syndrome Scale (PANSS; Kay et al., 1987) "P3: hallucinations" score. These individuals were compared to 32 controls with no history of psychiatric illness (Control group). Demographic and symptom information for participants is reported in Table 1. The groups did not differ in age, $F(2, 76) = 1.47$, $p = 0.24$, or handedness, $\chi^2(2) = 1.36$, $p = 0.51$, but did differ in sex, $\chi^2(2) = 7.58$, $p < 0.05$, and years of education, $F(2, 67) = 5.40$, $p < 0.01$. Specific group differences were assessed with Tukey's HSD used to correct for multiple comparisons when three groups were included in the analysis. With respect to patient group differences in symptom ratings, $p < 0.01$ was used as a cut-off for significance as a compromise between Type I and Type II errors. These individuals participated in one of two studies at the Neuroimaging Center (University Medical Center Groningen), in which the metrical stress evaluation task was administered (Vercammen and Aleman, 2010; Vercammen et al., 2010; Ćurčić-Blake et al., 2013). All participants provided written informed consent.

2.2. Design and procedure

2.2.1. Metrical stress task

Details regarding the design of the task have been published previously (Ćurčić-Blake et al., 2013); a summary is presented here (see Fig. 1). While undergoing fMRI, all participants were shown 48 two-syllable Dutch words, which appeared on a screen for 2 s and were followed by a fixation cross for 3 s. Each word was presented twice: once in the "phonological" condition, in which participants had to judge whether the metrical stress fell on the first or second syllable, and once in the "semantic" condition, in which participants had to evaluate whether the word presented had positive or negative valence. The stimuli were presented in 60 s blocks consisting of 12 word/fixation cross combinations, alternating between the phonological metrical stress (4 blocks) and semantic judgement (4 blocks) conditions. These eight blocks were interspersed with 7 baseline conditions, consisting of a fixation cross presented for a duration of 30 s. This resulted in a total of 11.5 min per run [(2 s stimulus + 3 s fixation cross * 12 trials * 8 blocks) + 3.5 min fixation]. Subjects responded by pressing the appropriate button (e.g., index finger: first syllable/positive valence; middle finger: second syllable/negative valence) on a button box with their right hand.

2.2.2. Image acquisition and pre-processing

See the Supplementary Materials for image acquisition and pre-

Table 1
Positive and Negative Syndrome Scale (PANSS) and demographic information. Means are reported with standard deviations (in brackets).

	Controls ($n = 32$)	NoAVH ($n = 26$)	AVH ($n = 21$)
Age	31.00 (9.34)	30.96 (6.00)	35.14 (12.81)
Range	18–52	22–44	19–61
Years of education[†]	12.93 (2.52)	12.42 (2.81)	10.44 (2.26)[*]
Sex (male:female)	19:13	22:4[††,¶]	10:11
Handedness,left:right	4:28	2:24	4:17
P1. Delusions		2.12 (1.21) [‡‡‡]	3.48 (1.37)
P2. Concep disorg		1.58 (0.9)	2.24 (1.26)
P3. Hallucinations		2.42 (1.39) [‡‡‡]	5.24 (0.44)
P4. Excitement		1.19 (0.63)	1.52 (0.81)
P5. Grandiosity		1.81 (1.36)	2.1 (1.34)
P6. Suspiciousness		1.88 (1.11) [‡‡]	2.9 (1.14)
P7. Hostility		1.08 (0.27)	1.1 (0.3)
N1. Blunted affect		2.5 (1.21)	2.57 (1.12)
N2. Emotional withdrawal		2.23 (0.91)	2.14 (0.73)
N3. Poor rapport		1.62 (0.94)	1.81 (0.81)
N4. Social withdrwl		2.27 (1)	2.43 (0.93)
N5. Difficulty abstr		1.54 (0.86)	2 (1)
N6. Lack flow		1.77 (0.95)	1.81 (0.98)
N7. Stereotyp think		1.19 (0.49)	2 (1.23)
G1. Somatic concern		1.31 (0.62)	1.38 (0.74)
G2. Anxiety		1.96 (0.92) [‡‡]	2.81 (1.03)
G3. Guilt		1.62 (1.17)	2.71 (1.68)
G4. Tension		1.81 (0.63)	2.38 (0.97)
G5. Mannerisms		1.73 (1.04)	2.29 (1.27)
G6. Depression		2.23 (1.24)	2.9 (1.09)
G7. Motor ret		1.77 (0.91)	2.1 (1)
G8. Uncooperative		1.27 (0.72)	1.1 (0.3)
G9. Unusual thought		1.69 (1.01) [‡‡‡]	3.1 (1.45)
G10. Disorientation		1.04 (0.2)	1.1 (0.44)
G11. Poor attention		1.62 (0.8)	1.9 (1.04)
G12. Lack of insight		2.15 (1.35)	2.57 (1.12)
G13. Disturb volition		1.35 (0.69)	1.62 (0.81)
G14. Poor impulse con		1.15 (0.37)	1.29 (0.56)
G15. Preoccupation		1.19 (0.4)	1.52 (0.6)
G 16. Social avoid		1.27 (0.53)	1.76 (0.77)

[†] education information was missing for 4 controls, 2 NoAVH and 3 AVH participants.
[*] = AVH vs NoAVH and Control, $p < 0.05$;.
[††] = NoAVH vs Control, $p < 0.01$;.
[¶] NoAVH vs AVH, $p < 0.05$;.
[‡‡] NoAVH vs. AVH, $p < 0.01$;.
[‡‡‡] NoAVH vs. AVH, $p < 0.001$.

processing information.

2.3. Data analysis

Data were analyzed as events using the publicly available group fMRI-CPCA (www.nitrc.org/projects/fmricpca); the theory and methods underlying fMRI-CPCA have been published extensively in previous work (e.g., Lavigne, Metzak, et al., 2015; Metzak et al., 2011; Woodward et al., 2015). Briefly, fMRI-CPCA integrates multivariate multiple regression analysis and principal component analysis (PCA) into a unified framework. Multiple brain networks are computed using PCA on task-timing-predictable variance in BOLD signal. Brain networks derived from this analysis can be interpreted spatially by examining the dominant patterns of intercorrelated voxels (derived from component loadings), and temporally by the networks' associated estimated HDR shapes (derived from predictor weights). Please see Supplementary Materials for a detailed explanation of fMRI-CPCA and full set of matrix equations (equations 1a – 4b).

2.3.1. Finite impulse response (FIR) model

Functional brain networks derived from fMRI-CPCA are obtained by performing a PCA on the BOLD signal variance constrained to that which is predictable from task timing. A FIR model (Henson et al., 2001; Serences, 2004) is used with fMRI-CPCA to separate out variance constrained to that which is predictable from task timing. This provides an estimate of the task-induced BOLD response at each post-stimulus time point and for each subject separately, averaged over trials, without making any *a priori* assumptions concerning the shape of the HDR. Eight post-stimulus time bins corresponding to the 1st to 8th full brain scans following stimulus presentation were used (see Supplementary Material equations 1b, 2b and 4b). The repetition time (TR) for these data was 2.5 s, which resulted in an estimated BOLD signal over a 20 s time window (2.5 $s \times 8$ bins $= 20$ s), with the first time point corresponding to stimulus onset. This time window was chosen to encompass the entire course of the HDR elicited by the experimental task, including the return to baseline.

2.3.2. Predictor weights and cognitive function

Task-induced BOLD-signal changes are indexed by predictor weights, which produce the estimated task-based HDR changes for each component (i.e., network), as well as for each combination of judgment condition and subject (see Supplementary Material equation 4a and b), averaged over trials. These predictor weights are the weights that are applied to the FIR model columns to produce the component scores (see Supplementary Material equations 4a and b). Due to the set-up of the FIR model, HDR changes are estimated for each combination of subject and condition, and represent the progression of network-based coordinated activation changes over post-stimulus time points (Lavigne and Woodward, 2018; Percival et al., 2020; Sanford et al., 2020).

2.3.3. Mixed-model analyses of variance (ANOVAs)

Statistical analyses of subject- and condition-specific HDR shapes were carried out to test whether each functional network reflected a biologically plausible and reliable hemodynamic response, as well as to test for differences between conditions and groups. These analyses were carried out as $8 \times 2 \times 3$ mixed-model analyses of variance (ANOVAs) on each component, with Time (8 post-stimulus time bins) and Judgment (phonological, semantic) as the within-subject factors, and Group (controls, patients with AVH, patients without AVH) as the between-subject factor. Interactions involving the Group factor were interpreted by follow-up analyses involving simpler effects, such as inspecting sets of adjacent time bins to determine the dominant effects underlying the complex interaction (i.e., sets of 2×2 interactions; Woodward et al., 2015, 2016). Tests of sphericity were carried out for all ANOVAs, and Greenhouse-Geisser adjusted degrees of freedom were checked, but only original degrees of freedom are reported here, because degrees-of-freedom corrections for violations of sphericity did not affect the results.

3. Results

3.1. fMRI-CPCA results

Inspection of the scree plot of singular values suggested a three-component solution, and each of these putative networks exhibited a biologically plausible, reliable HDR shape as reported below. The FIR model accounted for 10.81 % of the variance in the overall BOLD signal. The orthogonally rotated (Metzak et al., 2011) principal components (brain networks) accounted for 16.1 %, 8.96 % and 6.43 % of task-related variance, respectively. The dominant brain regions and estimated HDR changes of each functional network are displayed in Figs. 2-4. Anatomical descriptions for each network are presented in the Supplementary Materials in Tables S1, S3 and S5.

3.1.1. Component 1: multiple demand network (MDN)

Component 1 (see Fig. 2A) was an early-peaking network (see Fig. 2B) dominated by activity (positive loadings) in the paracingulate gyrus (BA 32), left precentral gyrus (BA 6), bilateral lateral inferior occipital cortex (BA 19), and bilateral superior parietal lobule (BA 7), an

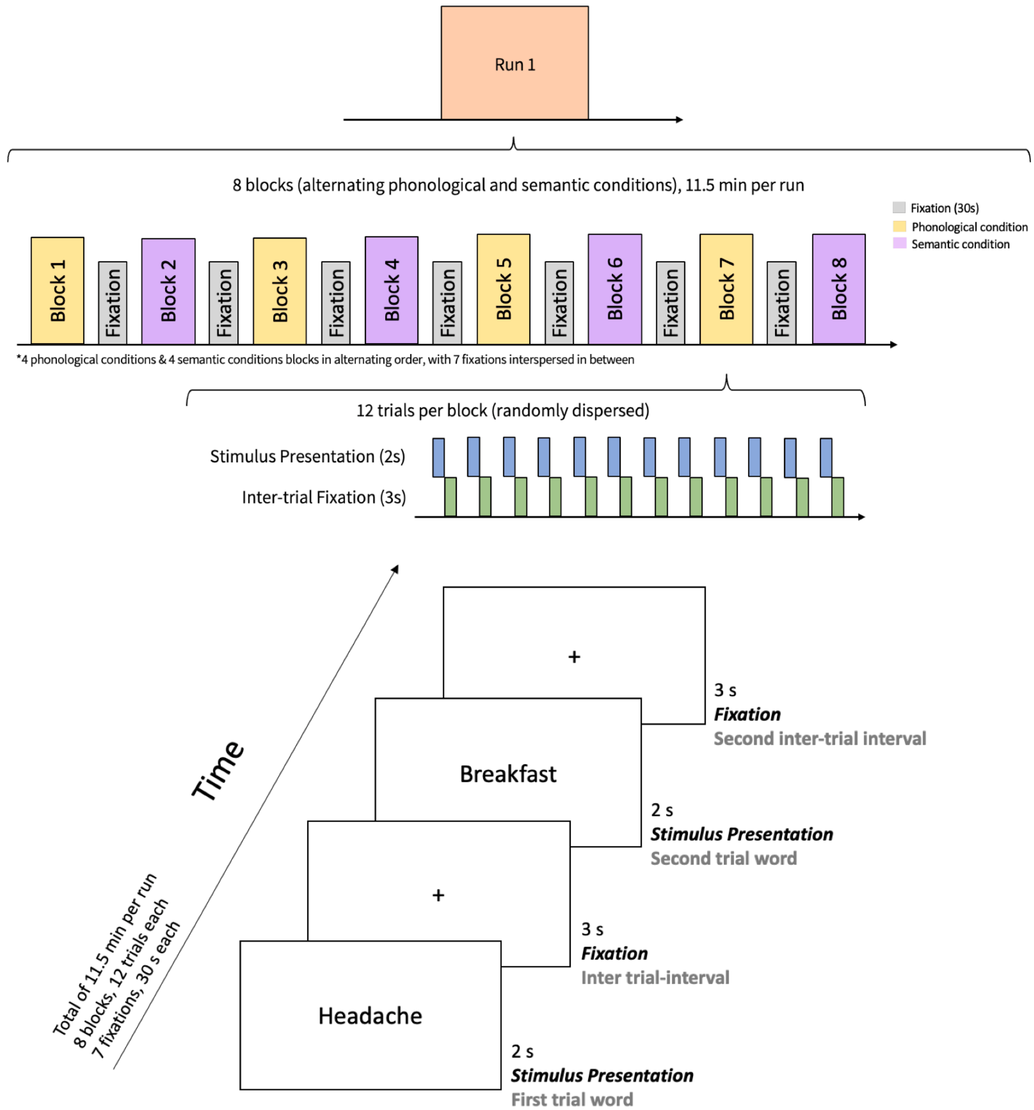

Fig. 1. A (top): Overview of metrical stress task trial and run organization. The stimuli were presented in 60 s blocks consisting of 12 word-fixation-cross combinations, alternating between the phonological/metrical stress (4 blocks) and semantic judgement conditions (4 blocks). These eight blocks were interspersed with 7 baseline conditions, consisting of a fixation cross presented for a duration of 30 s. B (bottom): Timeline of stimulus presentation. Each block began with 30 s of fixation. Next, one of the two-syllable Dutch words appeared on the screen for 2 s, followed by a fixation cross for 3 s. Each of the 48 words were presented twice; once in the "phonological" condition, in which participants had to judge whether the metrical stress was located on the first or second syllable, and once in the "semantic" condition, in which participants had to evaluate whether the word presented was positive or negative. In both conditions, subjects responded by pressing the appropriate button on a button box in their right hand.

anatomical pattern corresponding to the multiple demand network (MDN; Fedorenko et al., 2013; Zurrin et al., 2024). Cluster volumes for the most extreme 5 % of loadings for Component 1 are listed in Table S1. Detailed evidence for anatomical matches to published studies reporting the MDN is presented in Figure S1, and peak overlaps with resting-state networks arereported in Table S2.

Predictor weights associated with this network were entered into a mixed-model ANOVA and showed significant main effects of Time (8 post stimulus time bins, covering $8 \times 2.5\ s = 20$ s of task-induced HDR changes in post-stimulus time), $F_{7,532} = 29.74$, $p < 0.001$, $\eta_p^2 = 0.28$, indicating that the network reflects a reliable HDR shape. There was also a significant Time × Group interaction effect, $F_{14,532} = 4.06$, $p < 0.001$, $\eta_p^2 = 0.10$, and no other effects involving Group or Judgment were significant (all $ps > 0.23$), and no effects involving a Group × Sex interaction were significant (all $ps > 0.3$). The Time × Group interaction was not significant if the analysis was restricted to only the hallucinating and non-hallucinating groups ($p > 0.60$), therefore, they were averaged together for further analyses. This comparison of patients and controls resulted in a significant Time × Group interaction effect, $F_{7,539} = 7.47$, $p < 0.001$, $\eta_p^2 = 0.09$, which was followed up by repeated contrasts (comparing adjacent time bins). This analysis suggested that the Time × Group interaction was dominated by patient-control differences at the decrease from 6 s to 9 s, $F_{1,77} = 11.00$, $p < 0.005$, $\eta_p^2 = 0.13$, and the increase from 14 s to 16 s; $F_{1,77} = 12.97$, $p < 0.001$, $\eta_p^2 = 0.14$, reflecting the patient groups demonstrating a shallower reduction in the network below baseline compared to the control group (see Fig. 2B).

3.1.2. Component 2: language network (LN)

Component 2 (see Fig. 3A) was a mid-trial peaking network (see Fig. 3B) dominated by activity (positive loadings) in the left inferior frontal gyrus, pars opercularis (BA 38/47), occipital pole (BA 18) and left middle frontal gyrus (BA 45), all in alignment with the previously reported LN (Lipkin et al., 2022; Malik-Moraleda et al., 2022). Also present on this network were deactivation (negative loadings) in the precuneous cortex (BA 23) and lateral superior occipital cortex (BA 39) in a pattern matching the default-mode network (DMN; see Table S4,

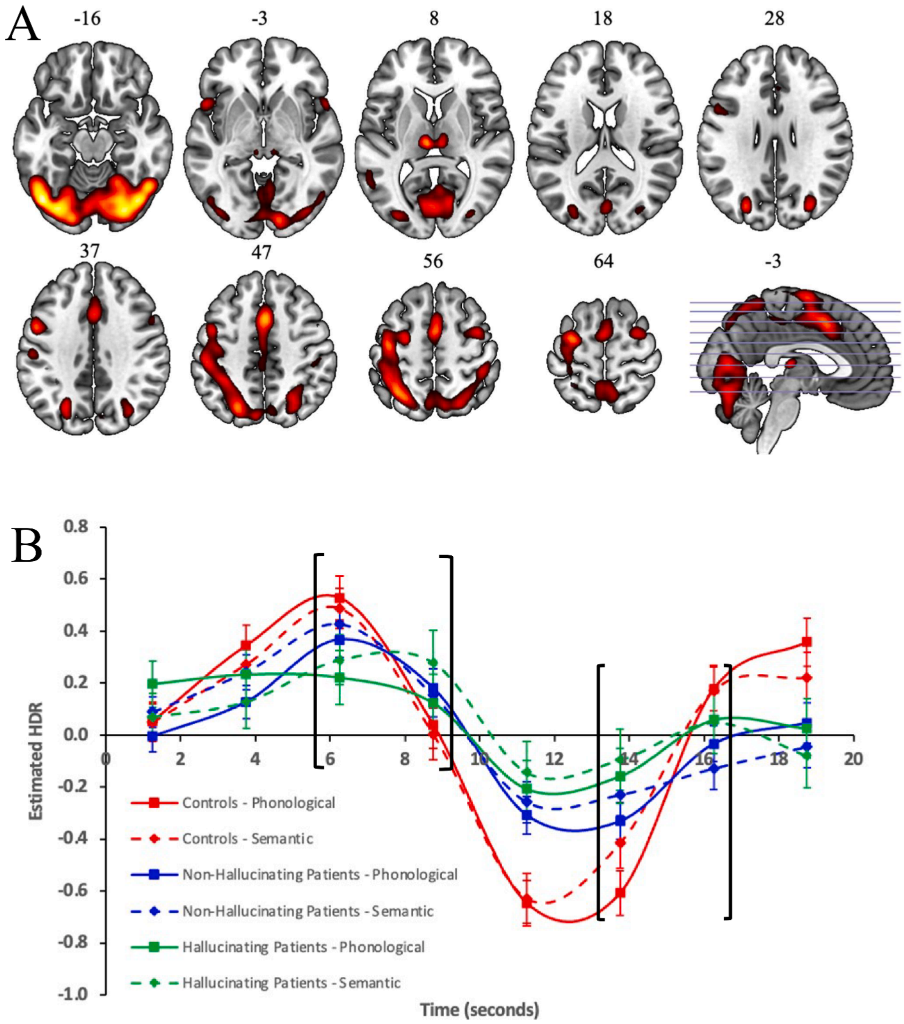

Fig. 2. Spatial and temporal features of Component 1 (Multiple Demand Network, MDN). A: Dominant 10 % of component loadings for Component 1 (red/yellow = positive loadings; threshold = 0.20, max = 0.28; no negative loadings passed threshold). Axial slices are located at the MNI Z-axis coordinates listed above brain slices. B: Mean finite impulse response (FIR)-based predictor weights for Component 1 for phonological/metrical stress and semantic judgement/semantic judgement trials for each group, plotted as a function of post-stimulus time. Brackets indicate the task-induced BOLD changes dominating the Time × Group interaction, due to the patient groups demonstrating a shallower reduction in the network below baseline compared to the control group.

negative loadings). Cluster volumes for the most extreme 5 % of loadings for Component 2 are listed in Table S3. Evidence for matches to published studies is presented in Figure S2, and overlap with resting-state networks is reported in Table S4.

Predictor weights associated with this network were entered into a mixed-model ANOVA and showed significant main effects of Time, $F_{7,532} = 71.80$, $p < 0.001$, $\eta_p^2 = 0.49$, and Group, $F_{1,76} = 7.32$, $p < 0.005$, $\eta_p^2 = 0.16$, whereby controls had higher activity (averaged over Time and Judgment) than non-hallucinating and hallucinating patients. The three-way Time × Group × Judgment interaction was also significant, $F_{14,532} = 2.60$, $p < 0.005$, $\eta_p^2 = 0.06$, as was the Time × Judgment interaction, $F_{7,532} = 2.60$, $p < 0.05$, $\eta_p^2 = 0.03$. No effects involving a Group × Sex interaction were significant (all $ps > 0.1$).

In order to interpret the Time × Group × Judgment interaction, we ran two Time × Group analyses for each Judgement condition separately. This resulted in a significant Time × Group interaction for the phonological condition, $F_{14,532} = 3.75$, $p < 0.005$, $\eta_p^2 = 0.06$, but not for the semantic condition, ($p = 0.23$). To interpret this, the Time × Group analysis was broken down into adjacent time bin contrasts for the phonological condition only, showing that the Time × Group interaction was dominated by change from 9 s to 11 s, $F_{1,77} = 4.27$, $p < 0.05$, $\eta_p^2 = 0.05$, and the decrease from 14 to 16 s, $F_{1,77} = 8.72$, $p < 0.001$, $\eta_p^2 = 0.10$. This was due to the peak being shallower for hallucinating patients relative to the other groups in the phonological/metrical stress condition, and a weaker reduction below baseline for hallucinating patients in that condition.

3.1.3. *Component 3: response (RESP)*

Component 3 (see Fig. 4A) was dominated by activity (positive loadings) in the bilateral anterior supramarginal gyrus (BA 40/2), left lateral inferior occipital cortex (BA 19), and left precentral gyrus (BA 6/48), all in alignment with previously reported networks involved in response (e.g., Fouladirad et al., 2022; Goghari et al., 2017, Component 1; Lavigne et al., 2016, Component 1; Lavigne and Woodward, 2018, Component 1; Sanford et al., 2020, multi-experiment Component 1; Woodward et al., 2015, Component 1). Also present on this network were deactivations (negative loadings) in the frontal pole (BA 10), lateral superior occipital cortex (BA 39), and precuneous cortex (BA 23) in a pattern matching the DMN (see Table S6, negative loadings). Cluster volumes for the most extreme 5 % of loadings for Component 3 are listed in Table S5. Evidence for matches to published studies is presented in Figure S3, and overlap with resting-state networks is reported in Table S5.

Predictor weights associated with this network were entered into a mixed-model ANOVA and showed significant main effects of Time, $F_{7,532} = 27.68$, $p < 0.001$, $\eta_p^2 = 0.27$, and Judgment, $F_{1,76} = 79.41$, $p <$

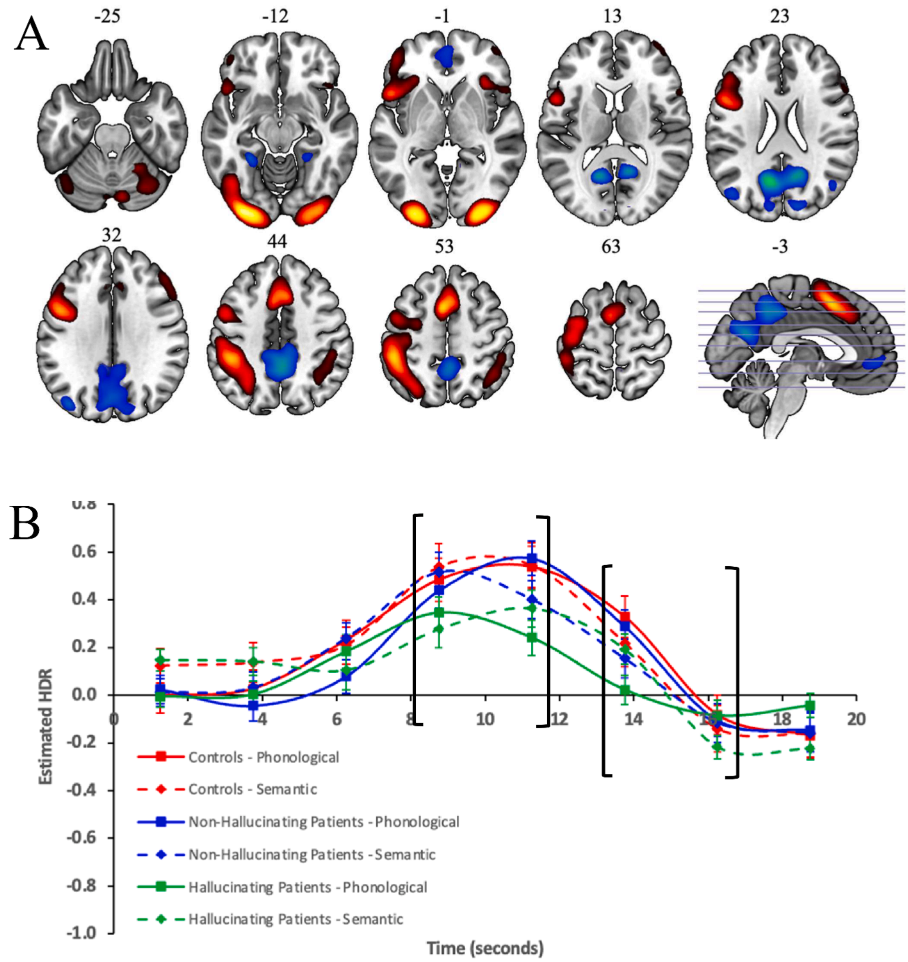

Fig. 3. Spatial and temporal features of Component 2 (Language Network, LN). A: Dominant 10 % of positive component loadings and dominant 10 % of negative component loadings for Component 2 (red/yellow = positive loadings; threshold = 0.17, max = 0.41; blue/green = negative loadings, negative threshold = −0.17, min = −0.29) Axial slices are located at the MNI Z-axis coordinates listed above brain slices. B: Mean finite impulse response (FIR)-based predictor weights for Component 2 for semantic judgement and phonological/metrical stress trials in each group, plotted as a function of post-stimulus time. Brackets indicate the task-induced BOLD changes dominating the Time × Group interaction for the phonological/metrical stress condition, due to the peak being shallower for hallucinating patients relative to the other groups in the phonological/metrical stress condition, and a weaker reduction below baseline for hallucinating patients in that condition.

0.001, $\eta_p^2 = 0.51$, as well as a significant Time × Judgment interaction, $F_{7,532} = 6.34$, $p < 0.001$, $\eta_p^2 = 0.08$. The Time × Judgment interaction was dominated by change from 14 to 16 s, $F_{1,76} = 5.11$, $p < 0.05$, $\eta_p^2 = 0.06$, showing a decrease for phonological/metrical stress and an increase for semantic judgement, due to an early suppression for semantic judgement that was not present for phonological/metrical stress. No main effects or interactions involving Group were significant for this component (all *ps* > 0.05).

4. Discussion

In the current fMRI study, coordinated activation in task-based macro-scale functional brain networks elicited by metrical stress evaluation (using a semantic judgement of positive versus negative valence as a control condition) was compared between hallucinating and non-hallucinating schizophrenia patients, and healthy controls. A LN emerged, and in the metrical stress/phonological condition only, hallucinating patients displayed an earlier and weaker peak activation, and shallower post-peak deactivation, in comparison to the non-hallucinating patients and controls (the reduced activation for hallucinations observed in the original ROI-based results were not specific to the imagery condition). MDN and RESP were also observed, but these did not display differences between hallucinating and non-hallucinating patients. This set of results suggests that, in addition to the well-documented hyperactivation of perception-based auditory networks, hypoactivation of internally focussed language-processing networks may also contribute to hallucinations.

The LN included the left inferior frontal gyrus, pars opercularis, that is often referred to as Broca's area (−51, 17, −1 in Table S3; row 3 in Table S4), a region commonly identified as involved in linguistic processes, such as controlled retrieval/selection of semantic information (Bunge et al., 2005; Thompson-Schill et al., 1997, 1999; Wagner et al., 2001; Woodward et al., 2015; Fedorenko et al., 2024) and auditory-verbal imagery (Aleman et al., 2005). It also included a region of the left middle temporal gyrus that is often referred to as Wernicke's area (−54, −43, 3; row 10 in Table S4), a region commonly identified as involved in perception and production language tasks in functional brain imaging studies (Price, 2012; Fedorenko et al., 2024). In addition, activity in the left middle frontal gyrus was observed (−48, 26, 26 in Table S3; row 8 in Table S4), which has been implicated in controlled selection and integration of semantic information (Badre et al., 2005; Bunge et al., 2005; Gold et al., 2006; Thompson-Schill et al., 1997, 1999; Fedorenko et al., 2024). In the current study, during the auditory imagery condition (metrical stress/phonological), hallucinating patients displayed an earlier and weaker peak activation and shallower post-peak deactivation, in comparison to the non-hallucinating patients and controls. This extends the findings of Ćurčić-Blake et al. (2013) by situating Broca's and Wernicke's area within a larger language network, and

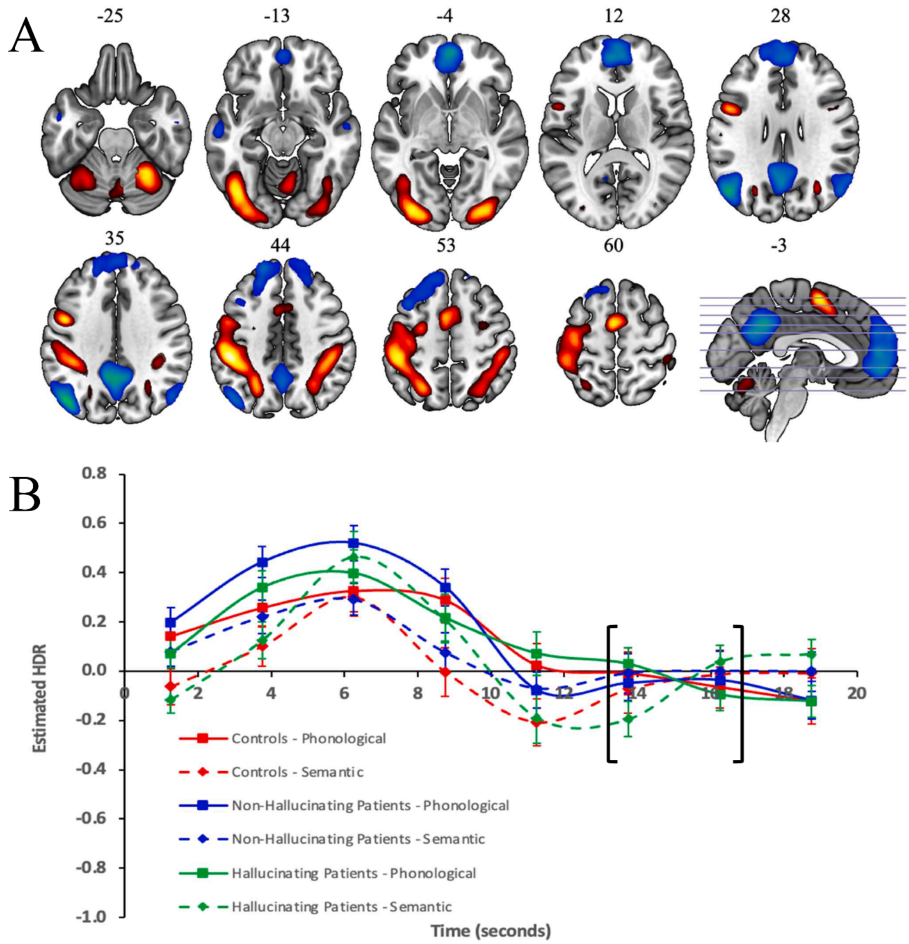

Fig. 4. Spatial and temporal features of Component 3 (Response, RESP). A: Dominant 10 % of component loadings and dominant 10 % of negative component loadings for Component 3 (red/yellow = positive loadings; threshold = 0.15, max = 0.28; blue/green = negative loadings, negative threshold = −0.15, min = −0.26) Axial slices are located at the MNI Z-axis coordinates listed above brain slices. B: Mean finite impulse response (FIR)-based predictor weights for Component 3 for semantic judgement and phonological/metrical stress trials in each group, plotted as a function of post-stimulus time. Brackets indicate the task-induced BOLD changes dominating the Time × Judgment interaction, showing a decrease for metrical stress and an increase for semantic judgement, due to an early suppression for semantic judgement that was not present for phonological/metrical stress.

showing hypo-activation among schizophrenia patients with hallucinations restricted to the metrical stress/phonological condition, whereas in the previous study a difference between conditions was not observed.

The hypoactive LN, as was observed in the present study, combined with the previously reported hyperactive STG/auditory perception network (Allen et al., 2008) can be related to cognitive accounts suggesting that AVHs arise from an imbalance between internal and external sources in source monitoring, in which the balance is shifted away from internal processing (hypoactivity of the LN) and towards external processing (hyperactivity of the STG), with AVHs being symptomatic of this imbalance (Larøi and Woodward, 2007; Woodward and Menon, 2013). Under the source monitoring cognitive model, the asymmetry created by the over-active 'external' network (i.e., the STG network) and the under-active 'internal' network (i.e., the LN) may cause internally generated events to be more likely to be mistakenly identified as arising from an external source (Larøi and Woodward, 2007; Woodward and Menon, 2013). It has been observed that internal attentional processing can move activity from the STG to the LN (including Wernicke's area) networks (Zatorre, 2007; Johnson and Zatorre, 2005; Halpern et al., 2004), providing support for an account holding that hypoactivation in the LN may lead to hyperactivation in the STG, as a weakened LN may lead to an incomplete shift of activation away from the STG.

In the MDN, we observed that healthy controls substantially deactivated this attentional functional brain network to below baseline late in the trial, which may be due to a shift from the MDN (peak 6 s) to the internal processing characteristic of the LN (peak 11 s), with this deactivation relative to baseline (12–13 s) not present for patients regardless of condition (phonological or semantic). We have reported a similar pattern in past work using the fBIRN oddball task (Lavigne et al., 2016). In both studies, schizophrenia patients demonstrated a shallower reduction below baseline compared to the control group. This suboptimal activation/deactivation is congruent with other tasks requiring suppression of non-targets (Hahn et al., 2010; Hepp et al., 1996; Hutton and Ettinger, 2006; Jimenez et al., 2016; Servan-Schreiber et al., 1996; Xia et al., 2020) and observations of impairments in latent inhibition in patients with schizophrenia (Gray, 1998).

Regarding the DMNs observed in this study, two of the retrieved networks, RESP and LN, had prominent negative loadings in regions associated with the DMN (Raichle et al., 2001), both showing deactivation in the precuneus cortex (BA 23) and lateral superior occipital cortex (BA 39). However, the DMN deactivations reciprocal to the RESP network showed anatomical patterns that were distinct from the DMN deactivations reciprocal to the LN (see Supplementary Material Figure S4). Deactivation configurations associated with LPN have been referred to in other work as DMN-A (Du et al., 2023), and the deactivation configurations associated with the RESP network have been referred to in other work as DMN-B (Du et al., 2023). The anatomical patterns that clearly distinguish these two versions of the DMN are listed in the Supplementary Material (Figure S4A). We have also observed that DMN-A is reciprocally associated with the LN and DMN-B with RESP in other work (Percival et al., 2020), a pattern which hat should be investigated systematically in future work.

4.1. Limitations

A limitation of this study is that the STG was not retrieved due to the visual nature of the task, so its activation could not be directly compared to that of the LN to comprehensively relate the findings to the cognitive internal/external balance theory of hallucinations. The STG is only retrieved when linguistic stimuli is presented auditorily (Belin et al., 2000; Binder et al., 2000; Sanford et al., 2020, Component 7). For future studies, metrical stress and semantic judgements could be split into visual and auditory presentation, for which the auditory STG network would be added to the visually based LN networks reported here (Sanford et al., 2020, Figure S3, purple solid lines for STG network). It would be predicted that in hallucinating patients, the STG network would show hyperactivity, and the LN hypoactivity, although this may depend on sufficiently deep linguistic processing afforded by the task, such as for phonological stress.

Between-patient-group differences in symptom severity are listed in Table 1, and the patient groups differed on ratings of hallucinations (P3), delusions (P1, P6, G9), and anxiety (G2), with all measures of severity being higher for the hallucinations group. Therefore, in addition to hallucinations, delusions and/or anxiety could have also accounted for the reported effects. In order to assess such possibilities, future studies will require larger samples that allow formation of groups of, for example, hallucinating but not delusional patients, delusional but not hallucinating patients, and hallucinating and delusional patient groups.

4.2. Implications

This set of results suggests that hallucinations are associated with hypoactivation of the LN during internal imagery of phonology, combined with a hyperactive perception-based STG auditory network reported in the literature. The imbalance in network activations may provide a biological underpinning for the externalization bias observed in hallucinating patients with schizophrenia (Brookwell et al., 2013; Woodward and Menon, 2011; Woodward et al., 2007).

There are potential therapeutic implications to be drawn from the current study. Repetitive TMS (rTMS) has been heavily investigated as a treatment for AVHs, and despite mixed results, it appears there is at least a moderate effect (Demeulemeester et al., 2012; Slotema et al., 2012, 2014). Different frequencies of magnetic stimulation can have varying effects on cortical excitability, with low-frequency rTMS (1 Hz or less) reducing excitability and high-frequency rTMS (5 Hz and higher) increasing excitability. Importantly, TMS-induced changes in specific brain regions have been shown to spread to other strongly connected regions (Hampson and Hoffman, 2010). Potentially, high- and low-frequency rTMS could be used to increase the network-wide activation of the LN and/or decrease the activation of the STG auditory perception network. However, caution is required because the BOLD signal provides an indirect measure of brain activity, and it is unknown which neural nodes may be causal for the pattern of observed LN BOLD signal or hallucinations.

4.3. Conclusion

This updated analysis placed previous ROI-based results into a network context. Of three retrieved networks, hallucinating patients showed hypoactivation in only one, the LN, and this was specific to the auditory-verbal imagery (metrical stress) condition, a level of specificity not afforded in the previous results. The observed hypoactivation of the LN, combined with previously identified hyperactivation of the STG-based auditory perception network (Lavigne et al., 2015; Lavigne and Woodward, 2018), according with cognitive accounts of hallucinations, suggesting an asymmetry created by the over-active 'external' network (i.e., the STG network) and the under-active 'internal' network (i.e., the LN), resulting in a biological basis for the externalization bias observed in hallucinating patients with schizophrenia.

CRediT authorship contribution statement

Luca Besso: Writing – review & editing, Writing – original draft, Formal analysis. **Sara Larivière:** Writing – review & editing, Formal analysis. **Meighen Roes:** Writing – review & editing, Visualization, Formal analysis. **Nicole Sanford:** Writing – review & editing, Formal analysis. **Chantal Percival:** Writing – review & editing, Visualization, Formal analysis. **Matteo Damascelli:** Writing – review & editing, Visualization, Formal analysis. **Ava Momeni:** Writing – review & editing, Visualization, Formal analysis. **Katie Lavigne:** Writing – review & editing. **Mahesh Menon:** Writing – review & editing, Supervision. **André Aleman:** Writing – review & editing, Project administration, Methodology, Investigation, Funding acquisition, Data curation, Conceptualization. **Branislava Ćurčić-Blake:** Writing – review & editing, Project administration, Methodology, Investigation, Funding acquisition, Data curation, Conceptualization. **Todd S. Woodward:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Conceptualization.

Declaration of competing interest

The authors have no financial nor personal relationships with other people or organizations that could inappropriately influence or bias this work.

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Supplementary materials

Supplementary data associated with this article can be found, in the online version, at 10.1016/j.pscychresns.2024.111824.

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