

Fronto-Temporal Disconnection Within the Presence Hallucination Network in Psychotic Patients With Passivity Experiences

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Psychosis, characterized by hallucinations and delusions, is a common feature of psychiatric disease, especially schizophrenia. One prominent theory posits that psychosis is driven by abnormal sensorimotor predictions leading to the misattribution of self-related events. This misattribution has been linked to passivity experiences (PE), such as loss of agency and, more recently, to presence hallucinations (PH), defined as the conscious experience of the presence of an alien agent while no person is actually present. PH has been observed in schizophrenia, Parkinson's disease, and neurological patients with brain lesions and, recently, the brain mechanisms of PH (PH-network) have been determined comprising bilateral posterior middle temporal gyrus (pMTG), inferior frontal gyrus (IFG), and ventral premotor cortex (vPMC). Given that the experience of an alien agent is a common feature of PE, we here analyzed the functional connectivity within the PH-network in psychotic patients with ($N = 39$) vs without PE ($N = 26$). We observed reduced fronto-temporal functional connectivity in patients with PE compared to patients without PE between the right pMTG and the right and left IFG of the PH-network. Moreover, when seeding from these altered regions, we observed specific alterations with brain regions commonly linked to auditory-verbal hallucinations (such as Heschl's gyrus). The present connectivity findings within the PH-network extend the disconnection hypothesis for hallucinations to the specific case of PH and associates the PH-network with key brain regions for frequent psychotic symptoms such as auditory-verbal hallucinations, showing that PH are relevant to the study of the brain mechanisms of psychosis and PE.

Key words: psychosis/hallucinations/functional connectivity/disconnection/presence hallucination network/resting-state fMRI

Introduction

Psychosis is an abnormal mental state including hallucinations and delusions that characterize psychiatric conditions such as schizophrenia.¹ It is broadly defined as a loss of contact with reality and may include abnormal sensations such as somatic passivity, thought withdrawal, thought insertion, delusions of being controlled, or auditory-verbal hallucinations (AVH), when in the form of voices commenting, conversing and audible thoughts. These specific psychotic symptoms, formerly known as Schneiderian first-rank symptoms,^{2,3} have been termed passivity experiences (PE),⁴ arguably reflecting a failure to self-attribute one's perceptions, thoughts, actions, or emotions.^{5,6} Related clinical research further suggested that PE and psychosis may be associated with impairments in self-monitoring,⁵⁻⁸ an essential aspect of sensorimotor functioning, based on sensorimotor and predictive mechanisms (ie, prediction of sensory consequences related to self-generated actions).⁹⁻¹¹ Disturbances in self-monitoring have been argued to reflect a diminished demarcation of the self-other boundary and often consist of at least 2 co-occurring, but phenomenally distinct aspects of positive symptoms. A reductive aspect is characterized by a loss in subjective experience, such as a loss of self-attribution (ie, sense of

agency or ownership); an additive aspect is characterized by the appearance of foreign or alien elements in subjective experience (ie, alien voices in AVH or alien thoughts in thought insertion). This classification, albeit being a phenomenological oversimplification, has recently been useful for the experimental investigation of thought insertion.¹² Thought insertion, is characterized by the experience that certain thoughts, occurring in one's mind, are not one's own thoughts (reductive aspect; loss of thought agency; or thought ownership).^{13,14} However, the lack of thought agency is not sufficient to account for thought insertion, because patients with thought insertion not only experience that their thoughts are not their own, but those of another alien person (additive aspect).^{15–18} The additive positive element is therefore also important, because lack of self-attribution (in thought awareness) also occurs in healthy subjects (as is the case of unbidden thoughts^{14,19}), whereas the additive aspect of thought insertion does not. A similar phenomenological dichotomy applies to AVH and other PE.

The large majority of previous neuroscience research of psychosis has targeted the first, reductive element of PE, characterized by lack or decreases of self-attribution,^{20–23} with very few studies on the second additive element of PE.^{4,24} Here we sought to target the second, additive, aspect of PE. Based on recent findings including behavioral, clinical, and imaging work^{4,25–27} it has been suggested that a particular complex symptom, presence hallucination (PH), and the associated neural system may be of relevance for psychosis, and especially the additive element of PE. PH is frequently observed in patients with schizophrenia²⁸ and is defined as the vivid sensation that another alien person is nearby when no one is actually present and can neither be seen or heard. PH has recently been linked to the disturbances in self-monitoring and sensorimotor processing^{4,25,26} related to bodily self-consciousness.^{25,29,30} Although PH occurs in around 50% of patients with schizophrenia, it is often overlooked in psychiatric patients²⁸ and it is accordingly not known how PH relates to PE in psychotic patients. However, PH is very frequent in patients with neurodegenerative disease suffering from hallucinations such as Parkinson's disease^{26,31} and dementia with Lewy bodies.^{32,33} PH has also been studied in neurological patients suffering from focal brain damage.^{31,34,35} Importantly, it has also been demonstrated that PH and somatic passivity, mental states that phenomenologically resemble PE, can be experimentally induced in healthy participants.²⁵ This controlled induction of a mild PE-like mental state was induced by robotically controlled sensorimotor stimulation, showing that PH are caused by the misperception of the source and the identity of sensorimotor signals of one's own body. The cortical network of neurological and robot-induced PH have been investigated recently by Bernasconi, Blondiaux et al²⁶ using lesion network mapping³⁶ and MRI-compatible robotics.³⁷ This led to the definition

of a PH-network, consisting of bilateral inferior frontal gyrus, posterior middle temporal gyrus, and ventral premotor cortex that was impaired in Parkinson's disease patients with symptomatic PH.²⁶ However, it is currently unknown whether the PH-network is impaired in psychotic patients with PE.

In the present study, we studied whether functional connectivity in the PH-network differed between a group of psychotic patients with symptomatic PE vs a group of psychotic patients without PE, allowing us to distinguish possible symptom-specific neural activities from disease-related effects. Based on the disconnection hypothesis in schizophrenia^{38–41} we hypothesized, first, to observe decreased functional connectivity within the PH-network, especially of fronto-temporal connections, based on previous findings linking impaired sensorimotor integration in schizophrenia.^{42–44} Second, using the whole-brain analysis we investigated whether the affected PH-network areas would be characterized by abnormal functional connectivity, especially with areas previously shown to be involved in PE.

Methods

Participants

Sixty-five psychotic patients were included in this study. Part of the sample of patients ($N = 23$) was recruited from the outpatient clinic of the department of psychiatry, Lausanne University Hospitals, Switzerland, and met DSM-IV criteria for schizophrenia or schizoaffective disorder.⁴⁵ Another part of the patients ($N = 42$), who met threshold criteria for psychosis, as defined by the "Psychosis threshold" subscale of the Comprehensive Assessment of At-Risk Mental States, were recruited from the TIPP Program (Treatment and Early Intervention in Psychosis Program, University Hospital, Lausanne, Switzerland).⁴⁶ Neurological disorders and severe head trauma were exclusion criteria for all patients. Informed written consent in accordance with institutional guidelines (protocol approved by the Cantonal Ethics Commission of Vaud, Switzerland) was obtained for all subjects.

Patients underwent an in-depth clinical assessment by a trained psychiatrist where the frequency and severity of symptoms were evaluated. Symptom severity was assessed in the patient groups using the Positive and Negative Syndrome Scale (PANSS).⁴⁷ PE were assessed based on the specific items of the Scale for the Assessment of Positive Symptoms (SAPS) (item 2: voices commenting; item 3: voices conversing; item 15: delusions of being controlled; item 17: thought broadcasting; item 18: thought insertion; item 19: thought withdrawal),^{4,48–51} as well as somatic passivity, audible thought and delusional perception (see [supplementary material](#) for a description of each symptoms). Patients were considered PE+ if they had presented at least one of these experiences

($N = 39$, 60% of tested patients; [supplementary table S1](#)) during the psychotic episodes. Twenty-six patients (40% of tested patients) did never show these symptoms and were thus included in the PE- group. The patient groups did not differ significantly on any demographic trait (see [table 1](#) for the details).

MRI was performed at the time of the patient's inclusion in the clinical program at Lausanne University Hospital. Therefore, the duration of the interval between the fMRI recording and the clinical assessment could vary between subjects. The mean time of this interval was 2.7 ± 2.2 years for all the participants (2.7 ± 2.3 year for the PE+ group and 2.6 ± 2.1 year for the PE- group) and did not differ between the groups ($t = -0.26$, $P = .8$).

MR Image Acquisition

MRI data were acquired using a 3 Tesla scanner (Magnetom TrioTim, Siemens Medical Solutions), equipped with a 32-channel head coil. Each MRI session included a magnetization-prepared rapid acquisition gradient echo (MPRAGE) sequence and a 9-minute gradient echo-planar imaging (EPI) sequence sensitive to BOLD (blood-oxygen-level-dependent) contrast. The MPRAGE acquisition had a 1mm in-plane resolution and 1.2 mm slice thickness, covering $240 \times 257 \times 160$ voxels (TR = 2.30 ms, TE = 2.98 ms, and TI = 900 ms). The functional MRI (EPI) acquisition had isotropic 3.3mm voxel size, with a 0.3mm inter-slice gap and covering a total of $64 \times 58 \times 32$ voxels (TR = 1920 ms and TE = 30 ms). Resting-state fMRI (rs-fMRI) was recorded; patients were instructed to lay quietly in the scanner with eyes open without focusing on any specific thought. The rs-fMRI sequence was performed at the beginning of the session, immediately after the structural scan acquisition and an experienced psychologist accompanied all patients during scanning. The acquisition process resulted in a sequence of 280 BOLD images for each participant.

Image Preprocessing

Standard preprocessing and data analyses were performed using SPM12 (fil.ion.ucl.ac.uk/spm/) and the functional connectivity toolbox CONN (conn-toolbox.org/) for MATLAB (mathworks.com). Functional images were corrected for slice time and motion, co-registered with a high-resolution anatomical scan, normalized into MNI space, resampled to $1.5 \times 1.5 \times 1.5$ mm³ and smoothed with a 6 mm³ full-width at half maximum (FWHM) Gaussian kernel for each subject. To estimate the excessive movement, mean frame-wise displacement (FD)⁵² during the scanning was estimated with the exclusion threshold of 0.5 mm. The groups did not differ in terms of the movements over the scanning period ($t = -0.35$, $P = .7$ with the mean FD of 0.18 ± 0.09 mm and 0.19 ± 0.1 mm for PE- and PE+ groups, respectively). The standard pipeline for confound removal of the CONN toolbox implementing a component-based noise correction procedure (CompCor) was followed.⁵³ Confounding effects of the individual time courses of the segmented white matter and cerebrospinal fluid, session effect of constant and linear BOLD signal trends, the 6 motion parameters with rigid body transformations and their first-order derivatives were extracted and regressed out of the data. Regressions were performed for the entire time-series. The BOLD signal data were passed through a band filter (0.009–0.08 Hz). A whole-brain mask in MNI space was used to restrict number of voxels tested during data analysis.

Networks

Presence Hallucination Network. The presence hallucination network (PH-network; [figure 1](#)) was established in an extensive previous investigation by Bernasconi, Blondiaux et al²⁶, by combining data from neurological patients with symptomatic PH and data from healthy subjects, in whom PH was experimentally induced during

Table 1. Demographic and Clinical Data of the Patients

Characteristic/Test	PE-	PE+	$P(t/\chi^2)$
Group size	26	39	
Gender, M/F	20/6	23/16	0.1 (2.2)
Handedness, R/L	23/3	34/3	0.4 (1.5)
Age, y	29.9 ± 10	30.5 ± 9.7	0.9 (-0.08)
Education, y	12.9 ± 2.5	12.3 ± 3.5	0.6 (0.55)
Illness duration, y	6.2 ± 7.7	5.2 ± 5.1	0.6 (0.6)
Chlorpromazine, mg/d	275 ± 247	365 ± 262	0.2 (-1.4)
PANSS total	65.5 ± 17.3	59.8 ± 16	0.2 (1.3)
PANSS positive	14 ± 4.9	13.5 ± 4.3	0.6 (0.4)
PANSS negative	17.5 ± 6	14.6 ± 5.8	0.06 (1.9)
Time difference between fMRI acquisition and symptom assessment, y	2.6 ± 2.1	2.7 ± 2.3	0.8 (-0.26)
Recruitment cohort (TIPP/Outpatient)	17/9	25/14	0.9 (0.01)

Note: Data are presented in mean \pm SD. Two-tailed t -tests and χ^2 tests performed when appropriate. M, male; F, female; R, right-handed; L, left-handed; PANSS, positive and negative syndrome scale; PE, passivity experiences.

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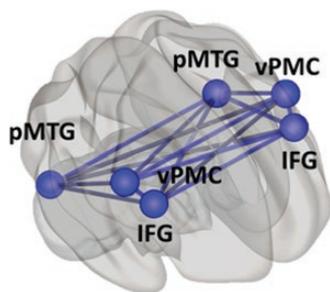


Fig. 1. PH-network. Projection on the brain surface of 6 regions forming PH-network: bilaterally inferior frontal gyrus (IFG), posterior middle temporal gyrus (pMTG), ventral premotor cortex (vPMC). The network forms 15 connections (lines). Based on Bernasconi, Blondiaux et al²⁶.

fMRI acquisition. The PH-network was defined as the overlap of the brain regions associated with experimentally induced PH (healthy subjects) and symptomatic PH (neurological patients).²⁶ The PH-network consisted of the bilateral posterior middle temporal gyri (pMTG; $x = \pm 54, y = -54, z = 0$), inferior frontal gyri (IFG; $x = \pm 51, y = 18, z = 29$) and ventral premotor cortices (vPMC; $x = \pm 26, y = -18, z = 57$).

Control Networks. Control regions were derived by shifting each region of the PH-network but keeping the same shape and the same number of voxels as the original network²⁶ (supplementary figure S1A). The areas were shifted to fit in the brain mask and do not comprise of white matter. The areas were shifted by the following coordinates: IFG $x \pm 20, y + 30, z - 15$; vPMC $x \pm 10, y + 30, z - 15$; pMTG $x, y + 30, z - 15$. A visual network from rs-fMRI network atlas⁵⁴ (supplementary figure S1B) was analyzed as an additional control network. It was comprised of 4 regions of interest (ROIs): calcarine sulcus, left thalamus, left and right middle/ superior occipital gyri.

Statistical Analyses

Demographic and Clinical Variables. Possible differences in demographic and clinical variables data between the 2 groups of patients were assessed by unpaired *t*-tests and Pearson's χ^2 tests, when applicable. Correlation analyses between the PANSS scores and functional connectivity of the PH-network connections were performed (supplementary material).

fMRI. Functional connectivity ROI-to-ROI analyses were conducted by extracting bivariate correlation values (z-transformed) for all possible connections within PH-network for each subject. Statistical analyses were performed in R (R-project.org/), v3.6. To investigate possible alteration in functional connectivity between groups of patients, we used linear mixed-effects models with Group (PE+, PE-) and Connection (15 connections) as fixed effects and Patients as a random effect. Post-hoc analyses for the between-group differences were performed with

FDR ($P = .05$) correction for multiple comparisons. Data outliers (6% of all data points) were removed based on 1.5IQR from the functional connectivity mean value for each connection. Patient's age and dose of medication were included in the analysis as covariates due to their considerable variance between the patients, which can influence functional coupling.^{55,56} In addition, PANSS positive and negative sub-scores, recruitment cohort (TIPP, outpatient), and the time difference between fMRI image acquisition and symptom evaluation were included in the model as covariates. Additional control analyses were performed by splitting the PE+ group according to the presence (PE+AVH+) or absence (PE+AVH-) of AVH to investigate whether the PH-network alterations were driven by AVH or by PE in general (supplementary material).

To further study functional connectivity associated with PH-network, we performed seed-to-whole-brain analysis. The ROIs from the PH-network, which connections showed significant functional connectivity differences between groups, were used as seeds. Individual correlation maps were created by extracting the mean resting-state BOLD time course from the seed region and correlating it with the time course of each voxel in the whole brain. Subsequently, correlation coefficients were normalized using Fisher-z-transformation to create individual single-subject maps of voxel-wise functional connectivity. The resulting maps were then entered in a second-level analysis. T-contrasts for group comparisons with $P < .001$ peak voxel-level uncorrected and cluster level FDR $P < .05$ corrected thresholds were analyzed. Age and medication dose of the patients were included as the covariates to control for possible confounds in functional brain coupling.

Spatial overlap. Spatial overlap analysis between the PH-network and language, auditory and default mode (DMN) networks (defined from rs-fMRI network atlas⁵⁴) was performed. See more details in supplementary material.

Results

Functional Disconnection Within the PH-Network

We observed a significant interaction between patient group and connection ($F_{(14,786)} = 3.4, P < .0001$), suggesting that specific connections of the PH-network are associated with PE. Yet, there was no significant main effect of patient group, meaning that there was no global difference of PH-network functional connectivity between groups (PE+ patients $r_{PH_total} = .21 \pm 0.26, CI(95\%) = [0.19, 0.23]$, PE- patients $r_{PH_total} = .24 \pm .28, CI(95\%) = [.22, .27]$, $F_{(1,56)} = 2.4, P = .12$). Post-hoc analysis showed that fronto-temporal connections, between the right pMTG and the right IFG ($r_{PE+} = .235 \pm .172, CI(95\%) = [0.17, 0.29]$; $r_{PE-} = .481 \pm .165, CI(95\%) = [0.40, 0.56]$; $t = -4.1, P_{FDR} = .0007$) and between the right pMTG and the left IFG ($r_{PE+} = -.029 \pm .223, CI(95\%) = [-0.10, 0.04]$; $r_{PE-} = .152 \pm .206, CI(95\%) = [0.07, 0.24]$; $t = -3.49,$

$P_{FDR} = .004$) (figure 2B) were reduced in PE+ compared to PE- patients. None of the other connections differed between groups. There also was an expected significant main effect of connection ($F_{(14,786)} = 52.4, P < .0001$), meaning that the strength of functional connectivity varied between the different connections of the PH-network independent of group.⁵⁷ The covariates (age, medication dose, PANSS positive, PANSS negative, recruitment cohort and time difference between scan acquisition and symptom evaluation) did not show significant effects (all $P > .25$, see supplementary material for the details). No significant correlations were observed between the PH-network right pMTG - right IFG, right pMTG - left IFG functional connectivity and PANSS positive, and negative scores (all $P \geq .1$, supplementary table S4).

The same analyses in control regions (main effect of group $F_{(1,52)} = 0.12, P = .73$; group by connection interaction $F_{(14,766)} = 1.4 P = .14$; supplementary figure S3) and in a visual control network (main effect of group $F_{(1,51)} = 0.33, P = .56$; group by connection interaction $F_{(5,267)} = 1.16, P = .32$; supplementary figure S4) revealed no significant differences between the 2 groups.

We further show that the fronto-temporal disconnection of the PH-network is driven by PE in general and not only by the presence of AVH (all $P \geq .1$) in PE + group (supplementary table S3, supplementary figure S5; more details in supplementary material).

Overlap analysis revealed that auditory and DMN networks do not overlap with the PH-network, whereas the language network overlapped in the left IFG and bilateral pMTG of the PH-network (supplementary figure S6).

Extended PH-Network Functional Connectivity Changes

To investigate whether there are any global changes in connectivity associated with the PH-network that differed

between groups, we conducted seed-based analyses from the 3 nodes forming the 2 altered connections in the PH-network indicated by the previous connectivity analysis. These 3 regions used as seeds were right pMTG, left IFG, and right IFG. With the right pMTG as seed, we observed a statistically significant decrease in functional connectivity between the right middle frontal gyrus and the left inferior frontal gyrus in the PE+ group compared to the PE- group. Both areas partly overlapped with the ROIs of the PH-network (108 voxels with the left IFG, 2 voxels with the right IFG; figure 3A). Using the right IFG as a seed, we observed a statistically significant decrease in functional coupling with the right medial superior frontal gyrus and the left Heschl's gyrus (superior temporal gyrus) in the PE+ group vs PE- group (figure 3B). Seeding from left IFG revealed a statistically significant increase in functional coupling with the left putamen and decrease in functional coupling with the left lateral occipital cortex (inferior occipital gyrus), and the right middle temporal gyrus in the PE+ vs PE- group (figure 3C). We note that the cluster in the right middle temporal gyrus was part of the PH-network area (59 voxels overlap with the right pMTG; figure 3A). The details of all clusters are described in table 2.

Discussion

Investigating functional connectivity changes within the PH-network in psychotic patients with and without PE, we observed an alteration of fronto-temporal functional connectivity within the PH-network that was characterized by decreased connectivity in PE+ compared to PE- patients. Additional results showed that this connectivity pattern is region-specific and limited to the PH-network as analysis of 2 control networks did not reveal any significant group differences. These data were corroborated and extended by seed-to-the-whole-brain connectivity,

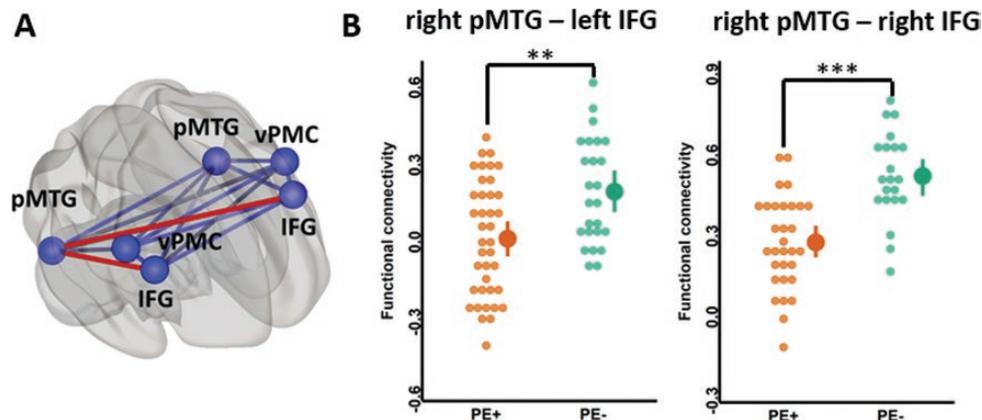


Fig. 2. Functional disconnection within the PH- network comparing patients with (PE+) and without (PE-) passivity experiences. (A) Abnormal fronto-temporal connections are marked in red and were decreased in PE+ patients vs PE- patients. (B) Functional connectivity between the right posterior middle temporal gyrus (pMTG) and the left inferior frontal gyrus (IFG; left plot), and the pMTG and the right IFG (right plot). Post-hoc FDR corrected at the threshold of $P = .05$. ** $P < .01$, *** $P < .001$. Dots represent the individual connectivity values of each patient.

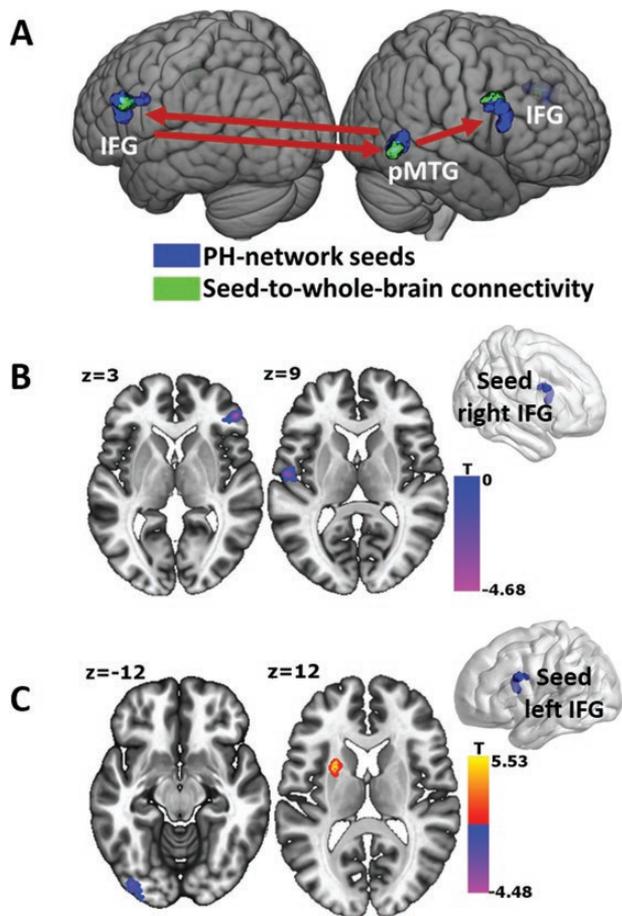


Fig. 3. Functional connectivity changes in PE+ vs PE- patients seeding from the PH-network areas to the whole brain. (A) PH-network seeds (in blue) were traced back during whole-brain functional connectivity analysis (areas in green). The red arrows represent from which seed (blue) the decreased functional connectivity in PE+ patients were observed. (B) Decreased functional connectivity in PE+ patients seeding from the right IFG with the right medial superior frontal gyrus and the left Heschl's gyrus. (C) Decreased functional connectivity in PE+ patients seeding from the left IFG with the left inferior occipital gyrus and increased functional connectivity with the left putamen. Voxel level $P < .001$ uncorrected, cluster threshold at $P < .05$ FDR corrected.

allowing us to trace back the fronto-temporal connectivity decreases in the PH-network without any *a priori* regional restriction of the connections.

Altered resting-state functional connectivity in psychotic patients has been observed in numerous studies (for review see^{41,58–61}) and it has been proposed that psychotic symptoms are related to decreases in functional connectivity formulated, eg, in the disconnection hypothesis.^{40,41,62,63} Our findings are compatible with and extend this proposal, as we observed reduced connectivity in PE+ patients that was restricted to the PH-network and concerned fronto-temporal connectivity within this network. Interestingly, fronto-temporal disconnectivity has previously been associated with impaired sensorimotor

integration in patients with schizophrenia.^{42–44} As PE^{4–6} and PH^{4,25} have also been associated with sensorimotor and prediction mechanisms, our finding of fronto-temporal disconnectivity in the PH-network in PE patients associates the brain mechanism of PH with those of PE and psychosis. Fronto-temporal disconnection of the PH-network in psychotic patients extends recent work investigating symptomatic PH in other patient populations, such as those suffering from Parkinson's disease²⁶ and dementia with Lewy bodies,³² 2 neurological neurodegenerative diseases that are frequently associated with hallucinations and psychosis. Thus, Parkinson's disease patients with symptomatic PH had decreased functional fronto-temporal connectivity (between the left pMTG and left IFG)²⁶ compared to Parkinson's disease patients without PH. Moreover, PH-network functional connectivity could be used to predict the occurrence of PH as a symptom during daily life and these patients were found to have abnormal elevated sensitivity to sensorimotor stimulation.²⁶ A PET study in dementia with Lewy bodies patients³² (who frequently experience PH) reported reduced glucose metabolism in fronto-temporal cortical areas (in patients with vs without PH), partly overlapping with the altered fronto-temporal connections in the present study. Taken together, the present findings suggest that fronto-temporal connectivity changes are not only of relevance to study PH, their neural mechanisms and disruption in neuropsychiatric diseases, but are also disrupted in psychiatric patients with psychosis suffering from a larger range of PE, extending the disconnection hypothesis to PH.^{42–44,64}

Prominent neurological work classified PH (following focal brain damage) consistently among disorders of the body schema and the bodily self (such as autoscopic phenomena).^{65–71} The felt presence is generally experienced as another person, but some patients have also reported to feel the presence of a second own body next to them.^{70,72,73} Moreover, some patients with PH may also report autoscopic phenomena such as heautoscopy or out-of-body experiences and other alterations of the body schema (for a detailed discussion of PH and its link to disorders of the bodily self see).^{70,74} More recent studies corroborated these findings, inducing PH repeatedly by electrical stimulation of a cortical region involved in sensorimotor processing³⁴ and linking PH to the misperception of the source and identity of sensorimotor signals in healthy participants^{12,25,27} and patients with symptomatic PH.^{4,26} The present findings associate the common symptom cluster of PE to neural mechanisms of PH, thereby providing further evidence for the prominent and long-standing proposal that a disturbed sense of self is of paramount importance in psychosis and schizophrenia^{75–77}; for recent discussion see.^{78–80} More recent work in schizophrenia reported behavioral alterations in bodily perception and experience, thereby providing empirical evidence that disturbances of body schema and

Table 2. Details of the Clusters From Seed-to-Whole-Brain Functional Connectivity Analysis

Seed-to-Whole-Brain PE+ vs PE-				MNI Coordinates				
BA	Anatomic Label		<i>k</i> (vox)	<i>x</i>	<i>y</i>	<i>z</i>	β	<i>T</i>
right pMTG								
9	Middle frontal gyrus	R	189	35	06	32	-0.22	-4.58
9	Inferior frontal gyrus	L	161	-53	17	27	-0.22	-4.47
right IFG								
8	Medial superior frontal gyrus (frontal pole)	R	137	48	39	3	-0.22	-4.64
43, 22	Heschl's gyrus (part of superior temporal gyrus)	L	149	-57	-11	9	-0.17	-4.06
left IFG								
	Putamen	L	178	-24	08	14	0.14	5.34
18	Lateral occipital cortex, inferior division (inferior occipital gyrus)	L	211	-39	-87	-12	-0.16	-4.18
21, 37	Middle temporal gyrus, temporooccipital part	R	147	63	-53	-3	-0.19	-4.13

Note: BA, Broadman area; *k*, cluster size in voxels; PE, passivity experiences. Voxel level $P < .001$ uncorrected, cluster threshold at $P < .05$ FDR-corrected.

self are impaired in psychotic patients,^{78,81} also suggested by the present findings.

One of the most frequent PE in psychosis is AVH,²⁸ often in the form of voices arguing and commenting about the patient. Among the many accounts for AVHs,^{61,82,83} a prominent one, that is of relevance for the present work on psychosis and PH, has argued that AVH are caused by altered self-monitoring associating loss of self-attribution (inner speech is not perceived as self-generated; negative aspect) with misattribution to an external agent (inner speech perceived as that of another person; additive aspect).^{84,85} At the neural level AVH have been associated with altered resting-state functional connectivity of the auditory, language and default mode (DMN) networks.^{86–88} Thus, how are AVH related to PH and to the neural mechanisms of PH? It could be argued that PH and the related PE are caused by brain mechanisms reflecting altered social processes, because PH has been linked not only to sensorimotor mechanisms and alterations of body schema,^{4,25,26} but also to social brain mechanisms.³¹ Concerning psychosis, such social mechanisms have also been underlined as an important pathomechanism, based on reports that AVH can be accompanied by co-perceived felt presences or social agents.^{89,90} Future work should carefully investigate the shared and distinct mechanisms between social and sensorimotor accounts of PH and their importance in psychosis. Concerning the overlap with other functional accounts of PH and psychosis, our analysis revealed no spatial overlap between the PH-network and the auditory network and the DMN, which both have been linked to psychosis.⁸⁸ We found minimal overlap with a language network previously linked to psychosis, suggesting possible links between PH and language networks commonly linked to AVH.^{88,91} However, the observed PH-network fronto-temporal connectivity differences were driven by the PE in general, rather than by the occurrence of AVH specifically as further analysis has revealed ([supplementary figure S5](#), [supplementary table S3](#), see more in

[supplementary material](#)). Further work is needed to directly investigate potential behavioral and neural overlaps between language and PH-related networks in psychosis.

Recent studies were able to link PH and mild psychotic states to altered sensorimotor processing and changes in voice perception. This was found in first-episode psychosis patients⁴ as well as healthy subjects.²⁷ Thus, when exposed to specific sensorimotor conflicts giving rise to PH, first-episode psychosis patients (with PE) misattributed their voice to an external agent. These misattribution errors were absent in patients without PE, showing that sensorimotor stimulations leading to a mental state mimicking PH is associated with alterations in auditory-verbal self-monitoring⁴ and, potentially, with the PH-network.

Our findings, through applying seed-to-whole-brain analysis, provide further evidence that PH, related sensorimotor mechanisms, and the PH-network are of importance in some forms of AVH (voices conversing, commenting, audible thoughts). When the affected PH-network areas were used as seeds to the whole-brain, we observed altered functional connectivity in key auditory regions. More specifically, we link the PH to auditory processing in psychosis patients by revealing altered functional connectivity between the PH-network and Heschl's gyrus. We found decreased functional connectivity (PE+ vs PE- group) between the right IFG and left Heschl's gyrus that is part of the primary auditory cortex and has frequently been reported to have altered functional connectivity in psychotic patients with AVH.^{63,92,93} Moreover, we observed increased functional connectivity between the left IFG and the left putamen in PE+ patients, a subcortical structure that has also been linked to AVH.^{94–96} AVH is one of the most common symptoms in psychotic patients²⁸ and indeed, in this study, one of the inclusion criteria for the PE+ group was the presence of AVH (characterized by voices conversing, commenting, or audible thoughts), where 56% of the patients reported to suffer from such AVHs ([supplementary table S1](#)). These findings, therefore, associate the PH-network

with some forms of AVH and extend proposals that the PH and related network is important for the additive aspect of AVH and PE.^{4,25,27} The seed-to-whole-brain data also corroborate behavioral evidence from specific sensorimotor stimulations that have been shown to not only induce experimentally-controlled PH, but also changes in auditory perception.^{4,27}

The current study had several limitations, which may restrict the interpretation of the results. First, the evaluation of the symptoms was considered as a lifetime occurrence. Although detailed interviews were carried out about all PE symptoms, we only had access to MRI data ranging over a large period of time. The time interval between the imaging and the PE assessment could vary between patients and we cannot state whether the participants were experiencing any of the PE at the time of the brain imaging session. Therefore, this study does not allow to answer the question whether brain activation is altered during an ongoing PE. However, it does show that the resting-state functional connectivity between brain regions previously associated with PH is impaired only in patients who have already presented PE. Future work should perform the clinical interview and scanning with a shorter and fixed delay. Second, future studies of the PH-network in psychosis should directly evaluate the occurrence of symptomatic PH, allowing comparisons of PE± patients with and without symptomatic PH and also investigating the neural correlates of experimentally induced PH and its comparison with symptomatic PH. We further note the lack of significant correlations between the PANSS and functional connectivity alterations (see [supplementary material](#) for more details) which would enable us to more directly link PH and the psychopathological profile of PE. Possibly, more refined measures specifically related to PE rather than psychotic symptoms in general are in need. However, in this study, we did not have access to any more refined measures related to the PE. Further research, beyond the present investigation, should be dedicated to study dynamic functional connectivity in relation to symptoms, such as PE and PH, and to the PH-network, potentially revealing temporal alterations of the networks we have defined here.

Conclusions

To summarize, we show that the brain regions and functional connectivity within the PH-network that was determined independently from the present study (experimentally induced PHs in healthy participants and symptomatic PHs in neurological patients)^{25,26} are of relevance in psychiatric patients suffering from psychosis characterized by PE. We found evidence for a specific decrease in fronto-temporal functional connectivity in psychotic patients with PE and that this decrease was driven by decreased connectivity between the right

pMTG and bilateral IFG. This PH-network connectivity decrease is of relevance to the PE in general, extending fronto-temporal alterations beyond AVH research.^{87,88,97,98} Besides, we show that the PH-network's altered connectivity is associated with changes in connectivity with Heschl's gyrus and putamen, 2 areas previously associated with AVH and altered auditory-verbal processing, further supporting the importance of the neural mechanisms of PH and PH-network in psychosis and PE. Based on the present data, future neuroimaging studies evaluating the sensitivity of psychotic patients to robot-induced PH^{25,26} and how this affects auditory-verbal processing^{4,27} will be necessary. This may allow for more detailed behavioral evaluations based on robot-induced mental states and their respective brain networks, providing improved biomarkers for diagnosis and therapy.

Supplementary Material

Supplementary material is available at *Schizophrenia Bulletin* online.

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