

## Altered Brain Long-Range Functional Interactions Underlying the Link Between Aberrant Self-experience and Self-other Relationship in First-Episode Schizophrenia

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**Self-experience anomalies are elementary features of schizophrenic pathology. Such deficits can have a profound impact on self-other relationship, but how they are related through aberrant brain function remains poorly understood. In this functional magnetic resonance imaging (fMRI) study, we provide new evidence for a cortical link between aberrant self-experience and social cognition in first-episode schizophrenia (FES). As identified in previous studies, ventral premotor cortex (vPMC) and posterior insula (pIC) are candidate brain regions underlying disturbances in both self-experience and self-other relationship due to their processing of predominantly externally guided (vPMC; goal-oriented behavior) and internally guided (pIC; interoception) stimuli. Results from functional interaction analysis in a sample of 24 FES patients and 22 healthy controls show aberrant functional interactions (background/intrinsic connectivity) of right vPMC and bilateral pIC with posterior cingulate cortex (PCC), a midline region that has been shown central in mediating self-experience. More specifically, our results show increased functional coupling between vPMC and PCC, which positively correlated with basic symptoms (subjective self-experience disturbances). pIC showed reduced functional coupling with PCC and postcentral gyrus and increased functional interactions with anterior insula. Taken together, our results suggest an imbalance in the processing between internally and externally guided information and its abnormal integration with self-referential processing as mediated by PCC. Due to our correlation findings, we suggest this imbalance to be closely related to basic symptoms in FES and thus anomalous self-experience. The findings further disentangle the cortical basis of how self-experience anomalies may pervade the social domain.**

*Key words:* psychosis/posterior insula/ventral premotor cortex/posterior cingulate cortex/functional magnetic resonance imaging/connectivity

### Introduction

Schizophrenia is a pervasive and complex neuropsychiatric disorder with basic deficits in self-experience that can have a profound impact on self-other relationship. Since the early 19th century, a crucial role has been attributed to the self and its prereflective attunement with the external world in schizophrenic psychopathology.<sup>1,2</sup> More recently, schizophrenia has been primarily characterized as a disorder of self-experience and awareness that entails anomalies in self-other relationship (see among others).<sup>3–8</sup> Self-experience deficits also have been approximated by basic symptoms, reflecting a variety of anomalies of subjective experience in the domains of cognition, perception, bodily experience, action, and emotion.<sup>9,10</sup> Disentangling the neural mechanism underlying an anomalous link between aberrant self-experience and self-other relationship will provide a better understanding not only of the nature of elementary features of schizophrenia but also of how the self-other relationship is grounded in self-experience.

Several empirical studies suggested that self-experience disturbances could be closely associated with anomalies in the self-other relationship. Schizophrenic patients with high self-monitoring skills were reported to have better social skills.<sup>11</sup> Others revealed confusion in the attribution of events to their origin, including the

attribution of self-produced sensory experiences and actions to external sources.<sup>12–17</sup> An increased tendency to incorporate the experiences of external bodies has been reported too. For instance, the rubber hand illusion (a condition in which an observed rubber hand is subjectively experienced as if it actually were one's own hand)<sup>18</sup> has been found enhanced in schizophrenic pathology.<sup>19,20</sup> Thus, along with anomalous self-experiences, social interactions may confuse with a blurred distinction between self and other.

In a previous functional magnetic resonance imaging (fMRI) study investigating social perception (observation of others' sensory-affective experiences),<sup>21</sup> we showed that deficits in self-other relationship in first-episode schizophrenia (FES) could have strong roots in disturbances of self-experience, including impaired multisensory integration and self-other distinction associated with ventral premotor cortex (vPMC) and posterior insula (pIC) dysfunction, respectively. Hence, abnormal functioning of these regions may be involved in the link between self-experience disturbances and some aspects of social dysfunction in schizophrenia.

From a general neurobiological point of view on schizophrenia, aberrant neural connectivity has been proposed as an elementary aspect in its pathophysiology.<sup>22–25</sup> Neuroimaging research seems to suggest a widespread and possibly context-independent alteration of functional connectivity in schizophrenia<sup>26–30</sup> and aberrant structural functional connectivity patterns.<sup>31,32</sup> Topologically, functional brain networks in schizophrenia could be characterized by a reduced clustering and small-worldness, associated with a less hub-dominated organization.<sup>33</sup> However, the specific links between neural connectivity and social dysfunction are poorly understood, partially due to a lack of systematic research on this topic.

This study aimed at providing more insight in how impairments in self-other relationship in schizophrenia could be related to altered functional interaction patterns. Specifically, we examined (1) whether vPMC and pIC could be characterized by altered neurofunctional interactions, (2) whether these could provide information complementary to task-evoked activation patterns, and (3) whether they could be related to symptomatology, especially disturbances of self-experience.

A peculiar role could be expected for posterior cingulate cortex (PCC) as one of the most central hubs in the human brain in terms of connectivity patterns.<sup>34,35</sup> PCC is a crucial node of the Default Mode Network,<sup>36,37</sup> allows the communication between different cortical modules or cross-network interactions<sup>38,39</sup> and is commonly implicated in schizophrenia.<sup>32,40</sup> Of particular interest in relation to the disability to distinguish between self and other in schizophrenia,<sup>41</sup> PCC often is associated with self-referential processing,<sup>42–45</sup> integrating self-experience,<sup>46</sup> and regulating the balance between internally and externally directed cognition.<sup>47,48</sup> The self also has been conceived

of as a basic precognitive structure related to such a balance as predisposed by the brain's intrinsic activity in cortical midline structures including PCC,<sup>42,49</sup> whereas abnormalities in intrinsic functioning of these structures have been linked with aberrant self-referential processing in schizophrenia.<sup>8</sup>

In order to address these issues, fMRI functional interaction analysis was performed on the same data set as used for our previous study<sup>21</sup> by measuring the statistical dependence between low-frequency blood oxygen level dependent (BOLD) signals across brain voxels (“background” or “intrinsic” connectivity).<sup>50,51</sup> Functional interaction analysis during specific task contexts also has been shown to be complementary to the analysis of task-evoked neural activation patterns.<sup>52,53</sup> Individual functional interaction indices were related to symptomatology, including positive and negative symptoms<sup>54</sup> and basic symptoms, ie, subjective disturbances of self-experience.<sup>9,55</sup>

## Methods

### *Participants*

Twenty-four outpatients with FES and 22 matched healthy control (HC) participants were included in this study and were the same as in Ebisch et al.<sup>21</sup> All participating FES patients had a history of a single psychotic episode, and all received a diagnosis of schizophrenia according to DSM-IV criteria 6 months after the episode. Detailed participant characteristics and inclusion criteria are described in the [supplementary material](#) and [table 1](#). FES patients were rated for symptom severity with the Positive and Negative Symptom Scale (PANSS)<sup>56</sup> and evaluated for the presence of basic symptoms by means of the schizophrenia proneness instrument—adult version (SPI-A)<sup>57</sup> by trained psychiatrists. The study was approved by the local Ethics Committee. Written informed consent was obtained from all participants after full explanation of the procedure of the study, in line with the Declaration of Helsinki.

### *fMRI Preprocessing and Analysis*

The same data set as in Ebisch et al.<sup>21</sup> was used for the present fMRI study. Data acquisition parameters and the first fMRI preprocessing procedures were the same. Additionally, for fMRI functional interaction analysis, a second step of data preprocessing was performed by using self-devised MATLAB scripts (The Mathworks Inc) including (1) bandpass filtering between 0.009 and 0.08 Hz<sup>51,58,59</sup>; (2) regression of global, white matter, ventricle signals, and their first derivatives<sup>50,60</sup>; (3) regression of 3-dimensional motion parameters and their first derivatives; (4) regression of task-related BOLD fluctuations<sup>50,52,61,62</sup>; and (5) scrubbing of motion-affected functional volumes.<sup>63</sup>

**Table 1.** Demographic Information About the First-Episode Schizophrenia (FES) Group and Healthy Control (HC) Group (Adapted from Ebisch et al, Soc Cogn Affect Neurosci 2013)

|   | FES Group ( <i>N</i> = 24)   | HC Group ( <i>N</i> = 22)                    |
|---|--|--|
| Age <sup>a</sup> (mean ± SD)  | 27.3 ± 4.8   | 27.5 ± 3.3                                   |
| Mean time from psychotic episode (months, mean ± SD)  | 8 ± 5  | n.a.   |
| Handedness score, <sup>a</sup> (mean ± SD)  | 65.3 ± 18.1  | 69.3 ± 15.8                                  |
| Male/female <sup>a</sup>  | 16/8   | 12/10  |
| Diagnosis   | (First-episode) schizophrenia  | n.a.   |
| Intelligence quotient (mean ± SD)   | 100 ± 8.5  | n.a.   |
| Empathy quotient, <sup>b</sup> mean ± SD (cognitive empathy <sup>c</sup> /emotional reactivity <sup>c</sup> /social skills <sup>d</sup> ) | 38 ± 11.4 (12.4 ± 5.4/12.2 ± 5.2/6.3 ± 2.8)  | 45.4 ± 9.7 (14.5 ± 4.6/14.6 ± 4.4/8.1 ± 2.3) |
| SCID-II Cluster A   | n.a.   | Negative                                     |
| SCID-II Cluster B   | n.a.   | Negative                                     |
| SCID-II Cluster C   | n.a.   | Negative                                     |
| PANSS Positive scale individual scores (mean ± SD)  | 16 10 9 14 17 16 21 14 12 16 18 12 10 12 13 11<br>19 13 8 13 9 10 11 15 (13.3 ± 3.4)             | n.a.   |
| PANSS Negative scale individual scores (mean ± SD)  | 8 10 10 9 10 11 12 16 12 24 12 8 10 9 11 11<br>22 9 14 9 8 12 22 (12 ± 4.5)                      | n.a.   |
| PANSS General Psychopathology scale individual scores (mean ± SD)   | 22 20 20 30 18 24 32 25 22 37 22 22 20 20 23<br>21 25 25 19 25 20 19 22 35 (23.6 ± 5)            | n.a.   |
| SPI-A total individual scores (mean ± SD)   | 138 28 74 91 115 71 67 5 0 114 40 36 97 17 12<br>27 42 22 83 82 45 40 49 85 (61.1 ± 38.4)        | n.a.   |
| Medication <sup>e</sup>   | 6 Quetiapine<br>7 Risperidone<br>3 Paliperidone<br>4 Aripiprazole<br>3 Olanzapine<br>1 Drug free | n.a.   |

Notes: SCID-II, Structured Clinical Interview for DSM-IV Axis II personality disorders; PANSS, Positive and Negative Symptom Scale; SPI-A, schizophrenia proneness instrument; n.a., not applicable.

<sup>a</sup>No significant differences between the HC and FES group.

<sup>b</sup>Significant difference between the HC and FES group ( $P = .02$ ).

<sup>c</sup>No significant differences between the HC and FES group.

<sup>d</sup>Significant difference between the HC and FES group ( $P = .02$ ).

<sup>e</sup>Clorpromazine equivalent mean dose = 422 mg/day, SD = 395.5 (calculated on 21 patients because no equivalents are available for paliperidone).

Seed-based analysis of long-range functional interactions was performed identifying temporally correlated patterns of brain activity across brain regions.<sup>50,64</sup> Functional interaction maps were calculated by means of voxel-wise, whole brain analyses for the 3 seed regions of interest (ROIs) defined as spheres with a 6-mm radius. ROI coordinates were based on Ebisch et al<sup>21</sup>: right vPMC (Talairach coordinates: 50, 7, 32) and bilateral pIC (Talairach coordinates: right pIC 38, -12, 7 and left pIC -38, -10, 7).

For all participants, we calculated correlations of BOLD fluctuations over continuous fMRI time series between the seed ROI time courses and the time courses of all individual brain voxels. After applying Fisher's  $r$ -to- $z$  transformation<sup>65</sup> to each correlation map, random-effect analysis was performed independently for each of the two groups in order to reveal functional interaction patterns that were consistent across participants. Statistical significance was determined by means of one-sample  $t$  tests. Group statistical maps were thresholded at  $P < .001$  corrected for multiple comparisons by the false discovery rate (FDR).<sup>66</sup>

To test for significant differences between the FES and HC groups, independent-samples  $t$  tests between the functional interaction maps for the 3 seed ROIs in right vPMC and bilateral pIC were performed. Statistical maps of these between-group contrasts were thresholded at  $P < .01$  FDR corrected with a cluster size of  $k > 8$ .

Additional ROI-based analyses were performed to investigate the relationship between functional interaction indices and symptomatology (SPI-A: basic symptoms; PANSS: positive, negative, and general symptoms) and to control for possibly confounding effects due to medication dosage (chlorpromazine [CP] equivalence values), illness duration, general cognitive ability (intelligence quotient [IQ]), task-evoked neural activation patterns. A priori ROIs were defined as spheres with a 6-mm radius and included the original seed ROIs (right vPMC, bilateral pIC) and the brain regions showing significant differences in coupling with the seed ROIs between the HC and FES groups (see table 2).

Consensus maps,<sup>67</sup> consisting of the sum of different binarized correlation maps (threshold corresponding to

**Table 2.** Location and Statistical Information Regarding the Voxel Clusters Showing Altered Functional Coupling With the Seed Regions of Interest (ROIs) in the FES Group, Compared With the HC Group

| Brain Region      | Talairach Coordinates | Cluster Size | <i>t</i> -value HC | <i>t</i> -value FES | <i>t</i> -value HC vs FES |
|-------------------|-----------------------|--------------|--------------------|---------------------|---------------------------|
| Seed ROI: RH vPMC |                       |              |                    |                     |                           |
| PCC               | 2, -32, 45            | 270          | -5.26              | 1.30                | -4.52                     |
| Seed ROI: LH pIC  |                       |              |                    |                     |                           |
| LH aIC            | -40, 22, 12           | 1512         | 0.82               | 8.66                | -4.81                     |
| RH aIC            | 44, 1, 15             | 540          | 3.12               | 11.07               | -4.44                     |
| PCC               | -1, -26, 45           | 270          | 8.06               | -0.81               | 4.36                      |
| RH PPC            | 38, -56, 33           | 135          | -7.18              | -2.36               | -4.32                     |
| LH PPC            | -34, -56, 24          | 324          | -4.57              | 1.87                | -4.58                     |
| RH aFC            | 32, 46, 24            | 2970         | -8.07              | -1.22               | -6.23                     |
| LH aFC            | -34, 46, 15           | 351          | -5.22              | 1.32                | -4.51                     |
| Seed ROI: RH pIC  |                       |              |                    |                     |                           |
| RH aIC            | 26, 19, 3             | 243          | -1.19              | 5.02                | -4.35                     |
| LH PostCG         | -49, -35, 48          | 432          | 5.47               | -0.50               | 4.12                      |
| RH PPC            | 29, -62, 24           | 702          | -4.57              | 1.99                | -4.65                     |
| LH PPC            | -34, -56, 26          | 324          | -7.50              | -0.23               | -4.46                     |

Note: RH, right hemisphere; LH, left hemisphere; vPMC, ventral premotor cortex; pIC, posterior insula; PCC, posterior cingulate cortex; aIC, anterior insula; PPC, posterior parietal cortex; aFC, anterior frontal cortex; PostCG, postcentral gyrus.

$P < .05$  FDR), allowed to test which voxel clusters showed altered functional connections in the FES group, compared with the HC group, in common between the seed ROIs (right hemisphere vPMC and bilateral pIC).

Detailed information about preprocessing and ROI-based analysis procedures is provided in the [supplementary material](#).

## Results

### *Functional Interaction Analysis: Between-Group Comparisons*

The functional interaction maps for the different seed ROIs calculated individually for the HC and FES groups are described in the [supplementary material](#) and visualized in [supplementary figure 1](#). Regarding between-group contrasts, seed-based, voxel-wise analysis of functional interactions yielded an increased functional coupling between the seed ROI in right hemisphere vPMC and right PCC in the FES group, compared with the HC group ([figure 1a](#), [table 2](#)).

With respect to the seed ROI in left hemisphere pIC, the results showed an increased functional coupling in the FES group with bilateral anterior insular cortex (aIC), bilateral posterior parietal cortex (PPC), and right anterior frontal cortex, whereas a decreased functional coupling in the FES group was detected between left pIC and right PCC, compared with the HC group ([figure 1a](#), [table 2](#)).

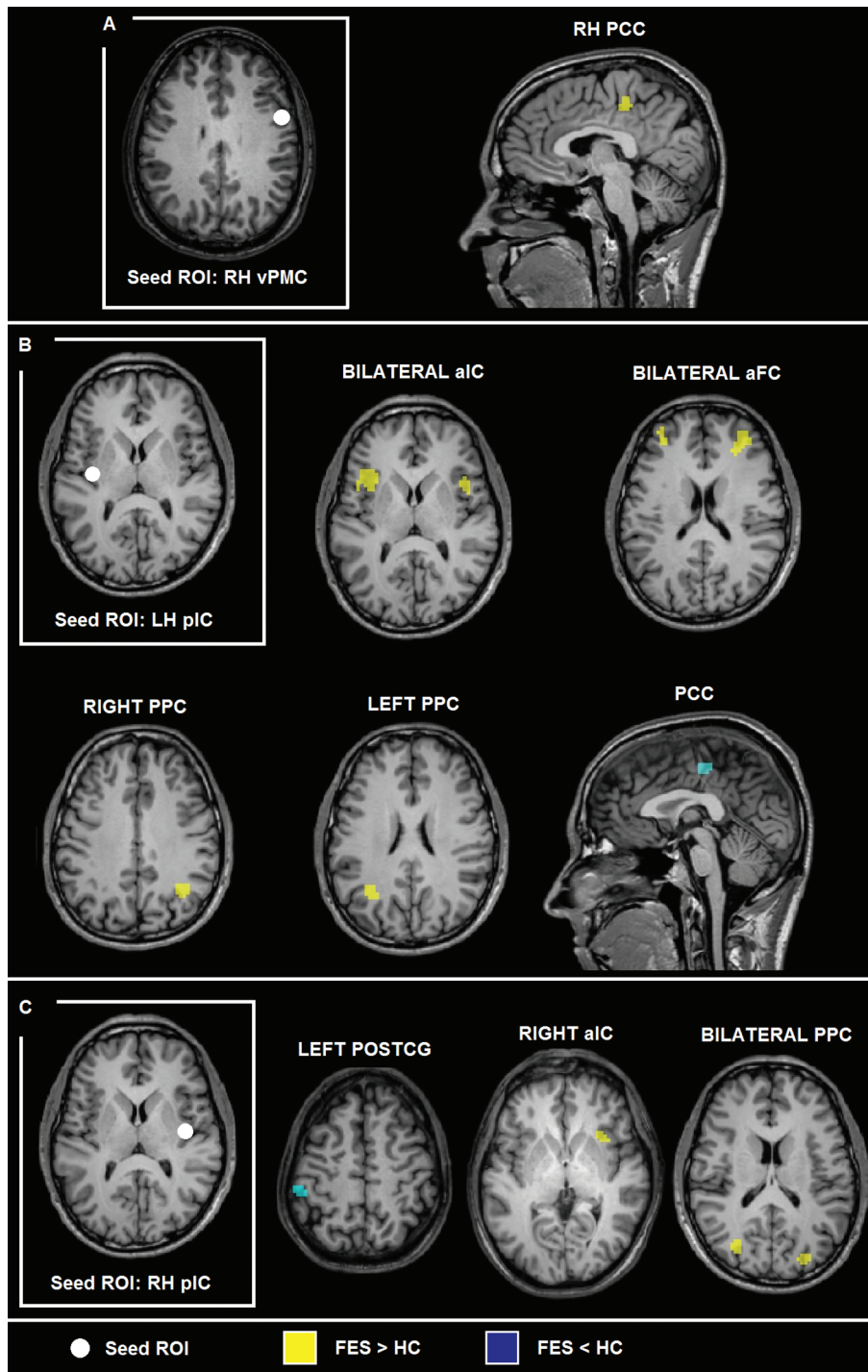
When using the right hemisphere pIC as seed ROI, we found increased functional interactions in the FES group with right aIC and bilateral PPC. We also found decreased functional coupling between right pIC and left postcentral gyrus (PostCG)/somatosensory cortex for the FES group, compared with the HC group ([figure 1c](#), [table 2](#)).

A ROI-based analysis of covariance of functional interactions between the seed ROIs (right vPMC, left pIC, right pIC) and the voxel clusters showing altered functional interactions in the FES group as detected by means of the voxel-wise functional interaction analyses showed that these alterations in the FES group were independent of BOLD responses to the experimental stimuli (task-evoked activation patterns) and of IQ. Further correlation analyses based on a similar ROI-based approach in the FES group showed that there was no significant, linear relationship between alterations in functional interactions in the FES group and CP, illness duration, or IQ (all  $r < 0.37$ ;  $P \geq .1$ ).

### *Relationship Between Functional Interactions and Symptomatology*

Applying an ROI-based approach, partial correlation analysis showed a significant relationship of functional interaction between right vPMC and PCC with basic symptoms in the FES group ( $r = 0.89$ ;  $P \leq .05$  FDR corrected), while excluding effects due to possible residuals of BOLD responses to the experimental stimuli, IQ, illness duration, and CP. No significant relationship was detected between vPMC functional interactions and PANSS scores (positive scale, negative scale, general psychopathology scale;  $P > .1$ ). Moreover, no significant relationship between symptomatology and long-range functional interactions was detected for the seed ROIs in left or right pIC ( $P > .1$ ).

Using a similar ROI-based approach, additional multiple regression with functional interaction indices as dependent variable and symptoms (basic symptoms as well as negative, positive and general symptoms) as independent variables showed that only basic symptoms



**Fig. 1.** Group statistical maps ( $P < .01$  false discovery rate corrected,  $k > 8$ ) showing altered functional connectivity patterns for (A) right ventral premotor cortex, (B) left anterior insula, and (C) right posterior insula in the first-episode schizophrenia group, compared with the healthy control group.

significantly predicted vPMC-PCC functional interaction in the FES group ( $\beta = .539$ ,  $P \leq .01$ ), but not PANSS scores (negative symptoms, positive symptoms, general symptoms, all  $P \geq .25$ ), confirming the specific relevance of basic symptoms.

A seed-based, whole brain covariance analysis with right vPMC as seed ROI and basic symptoms as covariate

confirmed a positive relationship ( $r > .62$ ,  $P < .001$ ,  $k > 5$ ) between right vPMC-right PCC coupling and basic symptoms (Talairach coordinates of PCC voxel cluster obtained by means of seed-based analysis: 7, -37, 45).

The relationship between vPMC-PCC coupling and basic symptoms is visualized in [figure 2](#) (left: ROI-based analysis; right: seed-based analysis).

### Functional Interaction Consensus Map

Consensus maps showed a voxel cluster in dorsal anterior PCC (ROI size = 243) characterized by altered functional interactions with 2 out of the 3 seed ROIs (2/3 consensus). Three voxels of the PCC cluster also showed altered functional coupling with all 3 seed ROIs: vPMC and bilateral pIC (3/3 consensus; Talairach coordinates: 2, -26, 45). [Supplementary figure 2](#) shows the consensus maps of the FES-HC contrasts for the 3 seed ROIs.

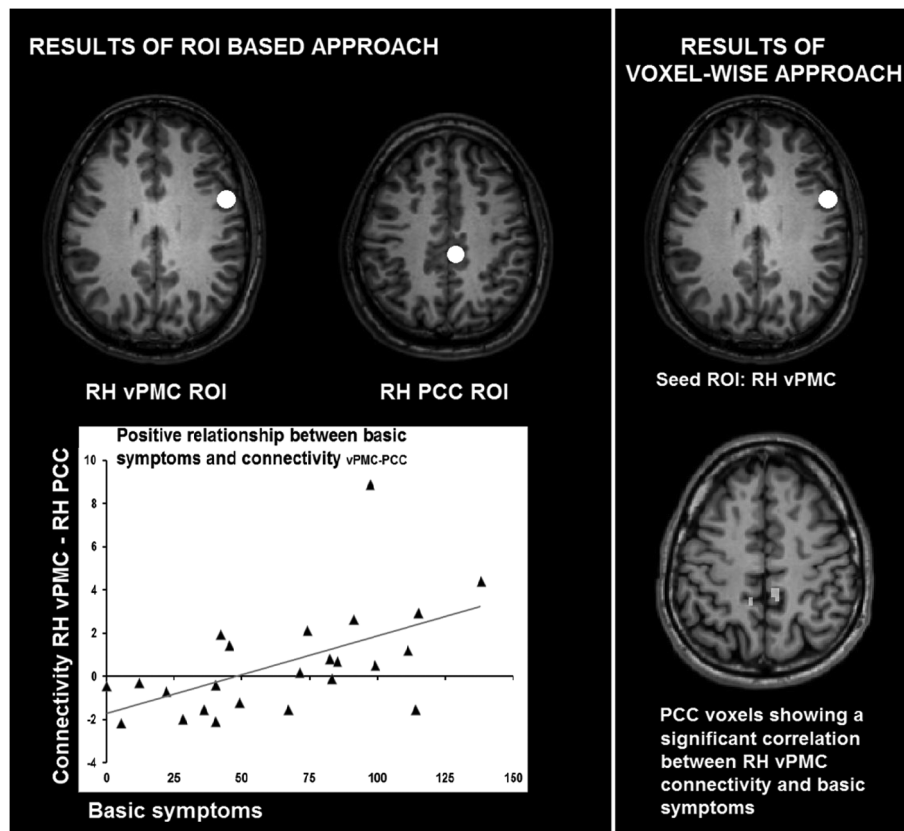
ROI-based analysis with right vPMC, bilateral pIC, and PCC (3/3 consensus) as a priori ROIs confirmed an altered functional coupling for the two ROI pairs left pIC-PCC and right vPMC-PCC ( $P < .05$  FDR corrected) in the FES group, whereas the difference between the FES group and HC group approached significance for the third ROI pair right pIC-right vPMC ( $P < .08$  FDR corrected).

### Discussion

This study aimed at investigating the functional interactions of right vPMC and bilateral pIC in FES. In accordance with the hypothesis, one of the main results regards an abnormal coupling of the seed ROIs with PCC in FES. First, functional interaction between vPMC and PCC significantly correlated with basic symptom severity. Second, consensus maps suggested that PCC could be a central

brain region underlying altered functional interactions of both vPMC and pIC. Control analyses demonstrated that the reported effects were independent of medication dosage (CP), illness duration, task-evoked neural activity, and general cognitive ability (IQ) and likely reflected functional abnormalities in the intrinsic functional organization of the brain in FES. Furthermore, a subdivision in different frequency bands of BOLD fluctuations<sup>68,69</sup> suggested that differences between FES and HC more specifically concerned the frequency range between 0.01 and 0.027 Hz (slow-5) but not the 0.027–0.07 Hz (slow-4) frequency range (see [supplementary material and supplementary table 1](#)).

PCC connectivity has been indicated consistently in schizophrenic pathology.<sup>70–73</sup> In this study, we found increased functional interactions between vPMC and PCC in the FES group. In line with previous studies on the intrinsic functional organization of the brain,<sup>60,74,75</sup> PCC and vPMC appeared to belong to distinct, possibly antagonistic functional networks in the HC group. Based on the functions of vPMC in multisensory integration, peripersonal space representation, and goal-directed behavior<sup>76–81</sup> and of PCC in mediating self-experience,<sup>43,45,46</sup> we propose that such a decreased functional segregation could lead to a deranged relationship between the intrinsic self (self-referential cognition) and the extrinsic self (the self interacting with the environment) in FES.



**Fig. 2.** The relationship between ventral premotor cortex-posterior cingulate cortex functional interactions and basic symptoms.

Interestingly, gamma amino butyric acid, an inhibitory neurotransmitter in the brain, in cortical midline structures including PCC likely has a relevant role in mediating between internally directed and externally directed thought,<sup>48</sup> providing a possible neurochemical basis of such alterations in FES.<sup>82</sup> Because cortical midline (PCC) and vPMC regions also have complementary functions in relating the self to its social environment,<sup>45,83–85</sup> altered vPMC-PCC interactions likely disrupt some aspects of social cognition too.

The detected positive correlation between vPMC-PCC coupling and basic symptoms highlights the clinical relevance of a reduced functional segregation between the two nodes in schizophrenia. Basic symptoms approximate subjective disturbances of self-experience.<sup>9,10</sup> This suggests that an abnormally strong vPMC-PCC coupling is related to a disrupted sense of a coherent self in everyday life. Interestingly, basic symptoms remain stable during the entire disease progression, including the prodromal phase of schizophrenia. Moreover, basic symptoms also represent a link between a more phenomenological European approach to psychopathology and a more categorical approach based on positive and negative symptoms typical of the Anglo-Saxon tradition. Specifically, basic symptoms, appearing more or less continuously even many years before psychosis onset, possibly are related to a predisposition and reflect the first changes in experience that set off the development of schizophrenic psychotic symptoms.<sup>86–88</sup> Indeed, the occurrence of a basic symptom could gradually increase in number and severity and, in most cases, ultimately develop into psychotic symptoms, such as negative and positive symptoms.<sup>87,88</sup> Hence, the study of their relationship with cortical processes has a peculiar relevance also from a clinical point of view, especially in the light of preventive approaches and an early diagnosis of schizophrenia.<sup>55,89</sup> In this light, it is recommended to apply the current approach to at risk of psychosis states and their transition to FES.

With respect to pIC, functional interactions with PCC and PostCG were decreased in the FES group. pIC is generally involved in processing somatosensory stimuli with affective or motivational significance and is considered a central brain region for interoception, self-awareness, and bodily awareness.<sup>90–95</sup> Regarding the social functions of pIC, in a previous study, we showed that pIC activity distinguished between self and other in social situations, especially where affective experiences are implicated.<sup>96</sup> Of particular relevance, this function appears disrupted in schizophrenic pathology.<sup>21</sup> The present findings of a diminished functional coupling in FES of pIC with PCC and PostCG, together representing a functional, sensory network in HC,<sup>47,97–100</sup> essentially extend these previous results in terms of pIC functional interactions underlying a deficit in the self-other distinction. Considering the sensory-affective functions of pIC and PostCG, and the mediation of self-experience in

PCC,<sup>43,45,46</sup> reduced integrity within this network arguably can be associated with a deficit in the processing of bodily sensory-affective information as belonging to the self.

Another remarkable finding was that the FES group exhibited a disproportionately strong coupling between pIC and aIC. Different from pIC, along with the integration of cognitive and emotional responses, aIC underpins the conscious evaluation of affective experience, ie, the subjective awareness of bodily feeling states.<sup>95,101,102</sup> Accordingly, insula abnormalities and deficits associated with insula damage, including disruption in self-awareness and self-other discrimination, are commonly reported in schizophrenic pathology.<sup>103,104</sup> Although pIC and aIC are anatomically connected,<sup>105,106</sup> in contrast to the present results in the FES group, functional connectivity studies in HC consistently suggest that they belong to distinct functional networks with minimal correlation of neural activity between them.<sup>97–100</sup>

Taken together, the altered pIC functional interactions reported in this study provide further evidence for an abnormal functional organization of neural networks involved in the awareness of the sensory-affective self. Such alterations could be at the basis of anomalous self-experiences commonly reported in schizophrenia, like ownership of experience and agency of action.<sup>104,107,108</sup> Regarding the social domain, insula dysfunction also could lead to difficulties in experiencing the self as distinct from the other.<sup>21,103</sup> For example, patients with schizophrenia may experience confusion in the attribution of internal sensory information to an external source or vice versa reflecting a blurred distinction between self and other.<sup>6–8</sup>

Finally, although in our previous study we provided evidence for impaired functioning of vPMC and pIC during social perception,<sup>21</sup> still little is known about how they might relate to each other. Aberrant functional connectivity of these regions has been implicated in schizophrenic pathology by previous studies.<sup>33</sup> Here we show that altered functional interactions of pIC and vPMC converged on PCC. Relevantly, PCC represents a cortical hub in the human brain mediating between activity in distinct networks.<sup>35,38,39</sup> As described above, on the one hand, dorsal anterior PCC has strong connections within the sensory network including pIC and PostCG.<sup>47</sup> On the other hand, it shows an antagonistic relationship with vPMC<sup>60</sup> involved in peripersonal space representation and goal-directed behavior.<sup>81,109</sup> Both relationships appear anomalous in FES. Therefore, the present results could reflect a neural mechanism underlying a deregulated interaction between an afflicted sensory-affective self and its environment with a central role of PCC.

Some additional issues need to be mentioned. First, the present fMRI data did not include a task-free condition. Possibly, conditions with systematic task demands modulate functional coupling.<sup>50,62</sup> It is recommended for

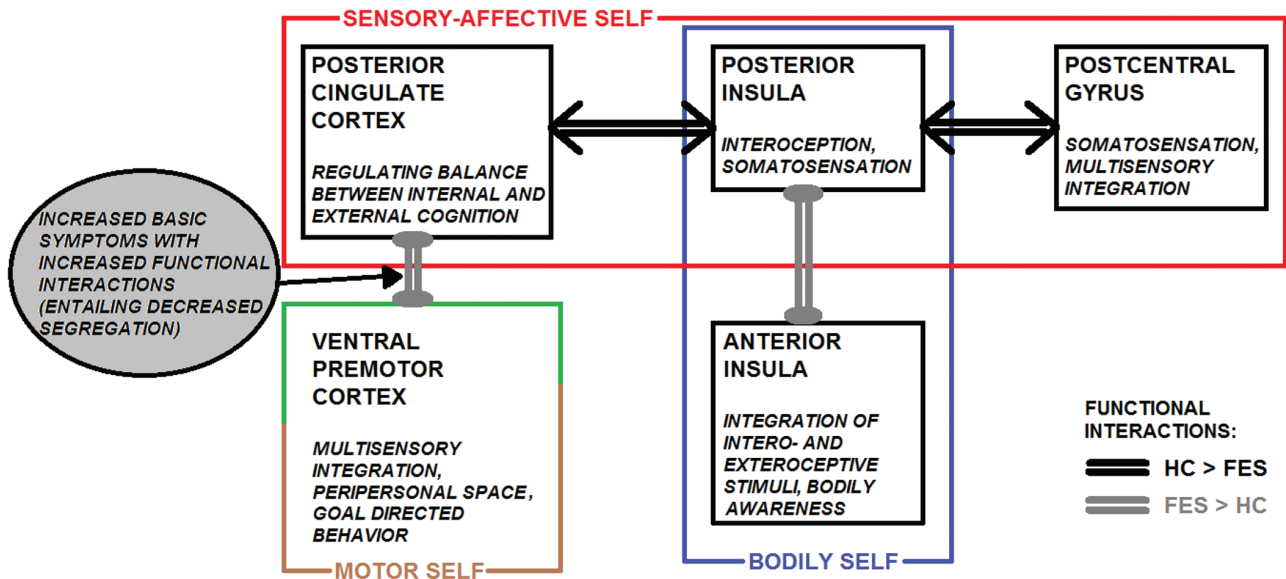


Fig. 3. Schematic representation of the general study results.

further studies to include task-free periods for elucidating whether aberrant functional interaction patterns in FES reflect an intrinsic, neural predisposition of the brain to abnormally react to social stimuli.<sup>110-112</sup> Nevertheless, given the regression of task-related BOLD signal and rigorous control analyses, we argue that it is very unlikely that the observed effects can be explained by task-evoked BOLD responses. Analysis of background functional interactions rather could provide information complementary to task-evoked BOLD responses in terms of brain long-range communication.

Second, no relationship was detected between brain long-range communication and positive and negative symptoms, and correlation between altered functional interaction and basic symptoms was independent of positive and negative symptoms. This may underscore the relevance and specificity of basic symptoms, tapping into distinct neural mechanisms. A possible alternative explanation is that the included patients had a very recent illness onset and relatively low PANSS scores. Further studies will be needed to investigate patients with more pronounced positive and negative symptoms and chronic samples for a better understanding of the relationship between psychotic symptoms and its progress over time.

Third, some previous studies showed that antipsychotic medication influenced functional connectivity of cortical networks,<sup>113,114</sup> suggesting that medication might have contributed to the results in this study. However, covariance and correlation analyses showed that altered functional interaction patterns in the FES group and their relation to symptomatology were independent of antipsychotic medication dosage. Moreover, the FES patients were treated by a single atypical antipsychotic drug for a relative short time. Therefore, we argue that it

is unlikely that the presented results can be attributed to medication effects.

Finally, although correlations with particular symptoms suggest that some alterations in functional interaction patterns are related to specific aspects of schizophrenic pathology, optimally an additional psychiatric, nonschizophrenic control group would have been needed to obtain greater specificity in associating the present results with FES.

In conclusion, this study demonstrates altered neurofunctional interactions of vPMC and pIC in FES, compared with HC, as reflected by a reduced segregation between and a reduced integration within functional networks associated with sensory-affective processing, self-awareness, and interaction with the external world (figure 3). The same networks also have important functions in social cognition and interaction. The results suggest imbalance in the processing between internally and externally guided information and its abnormal integration with self-referential processing as mediated by the PCC. This imbalance could be closely related to anomalous self-experience in FES.

### Supplementary Material

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

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