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Altered Neural Correlate of the Self-Agency Experience in First-Episode Schizophrenia-Spectrum Patients: An fMRI Study

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Background: **The phenomenology of the clinical symptoms indicates that disturbance of the sense of self be a core marker of schizophrenia.** ***Aims:*** **To compare neural activity related to the self/other-agency judgment in patients with first-episode schizophrenia-spectrum disorders (FES, *n* = 35) and healthy controls (HC, *n* = 35).** ***Method:*** **A functional magnetic resonance imaging (fMRI) using motor task with temporal distortion of the visual feedback was employed. A task-related functional connectivity was analyzed with the use of independent component analysis (ICA).** ***Results:*** **(1) During self-agency experience, FES showed a deficit in cortical activation in medial frontal gyrus (BA 10) and posterior cingulate gyrus, (BA 31; *P* < .05, Family-Wise Error [FWE] corrected). (2) Pooled-sample task-related ICA revealed that the self/other-agency judgment was dependent upon anti-correlated default mode and central-executive networks (DMN/CEN) dynamic switching. This antagonistic mechanism was substantially impaired in FES during the task.** ***Discussion:*** **During self-agency experience, FES demonstrate deficit in engagement of cortical midline structures along with substantial attenuation of anti-correlated DMN/CEN activity underlying normal self/other-agency discriminative processes.**

Key words: first-episode schizophrenia/neuroimaging/fMRI/self-agency/independent component analysis

Introduction

Sense of agency, the ability to distinguish actions and effects caused by oneself from events occurring in the external environment, is a fundamental aspect of human cognition. Underlying such function, self-monitoring processes are often assumed, in which predicted events accompanied by one's own volitional action are compared with actual events observed in the external environment.[1,2]

Recent concepts as discussed in neuroscience refer to "minimal self" that is "phenomenologically described as a consciousness of oneself as an immediate subject of experience, unextended in time."[3] "Minimal self" which is realized primarily in the sensory and motor domains, respectively, is also subject of study in this research. In contrast, other aspect of self "narrative self" represents a "more or less coherent self that is constituted with a past and a future in the various stories that we and others tell about ourselves."[3,4]

Anomalies of minimal self are apparently related to the phenomenology of first-rank schizophrenia symptoms, in which thoughts and actions are perceived to be under the control or influence of an external agent or where there is a loss of clear boundaries between the sense of self and others.[5,6]

Nevertheless, it has been postulated that a deficit in self-monitoring could underlie psychotic symptoms beyond the scope of Schneider's symptoms.[7] Indeed, the evidence at a meta-analytic level have shown that a deficit in self-monitoring is associated with auditory hallucinations per se.[8] An anomalous self-related experiences precede frequently the onset of psychosis by many years.[9] In addition, the self-monitoring deficit is detectable in unaffected siblings of patients with schizophrenia[10] and it could represent an specific endophenotype within the schizophrenia spectrum.

These and other evidence suggest a disturbance of the basic sense of self as a central feature of schizophrenia.[11]

Traditional tasks used in functional magnetic resonance imaging (fMRI) research may activate regions

implicated in the neurobiology of schizophrenia, but typically do not tap into the core phenotype of the illness.[12] Therefore, there is a great need for novel tasks, which would specifically challenge key symptoms of the disease. Exploring neural substrate of self-processing in schizophrenia would, for the reasons given above, provide valuable insight into the neurobiology of the disease.

Functional brain imaging studies in healthy controls (HC) confirmed that self-related processing may be specifically mediated by cortical midline structures (CMS). A wealth of studies summarized in several meta-analyses have demonstrated a predominant involvement of the anterior and posterior CMS (medial prefrontal cortex, anterior cingulate; posterior cingulate and precuneus) in the processing of self-specific stimuli that occurred across various functional domains in healthy subjects.[13–16] A widely used experimental design employed in those studies assess the neural bases of self-related processes using manipulations with the action-effect coupling either by systematically varying the delay, the morphology or the congruence of the visual feedback.[17]

Despite paucity of functional imaging studies focusing on self-agency (SA) in schizophrenia[18,19] it has been proposed previously that aberrant activity in CMS regions such as the default mode network (DMN) of individuals with schizophrenia can lead to a misattribution of internally/externally generated stimuli. This can result in symptoms such as thought insertion and delusions of control.[20]

Here, we present an fMRI event-related study of the self-agency/other-agency (SA/OA) judgment in first-episode schizophrenia-spectrum patients (FES) and in HC subjects.

First, we assessed the differences in brain activation between the 2 groups during an emergent SA/OA experience. As an impaired overall performance is inherent to a wide scope of cognitive tasks requiring a voluntary response in schizophrenia,[21] we minimized sources of performance's confounds at the level of task composition by use of self-paced fMRI design. Second, by the use of independent component analysis (ICA) we identified intrinsic neuronal networks responsible for SA/OA judgment and compared them between FES and HC.

Methods

Subjects

Thirty-five FES patients (table 1) diagnosed according to ICD-10. The diagnostic procedure was standardized with a structured MINI International Neuropsychiatric Interview.[22] fMRI was performed at the initial stage of second-generation antipsychotic therapy (mean 10 weeks of medication at the time of the study). Assessments included Positive and Negative Symptom Scale (PANSS).[23] All FES subjects were detected through their first hospitalization in the Bohnice psychiatric hospital with catchment area of 1 million inhabitants living in Prague and northern part of Central Bohemia.

Thirty-five HC subjects were recruited via a local advertisement; they had a similar sociodemographic background as the FES to whom they were matched by age, education and sex. HC were evaluated with modified version of MINI and were excluded if they had a lifetime history of any major psychiatric disorder or a family history of psychotic disorders. All subjects were right-handed as confirmed by Edinburgh Handedness Inventory.[24] The exclusion criteria for groups included a history of seizures or significant head trauma, mental

Table 1. Sociodemographic and Clinical Data for the First-Episode Schizophrenia-Spectrum and Healthy Control Groups

	FES (n = 35)	HC (n = 35)	P Value (2-tailed t test)
Age, years; mean (SD)	29.4 (6.7)	30.6 (9.2)	.56
Female, no. (%)	17 (48.6)	21 (61.2)	.34[a]
Male, no. (%)	18 (51.4)	14 (38.8)	
Schizophrenia, no. (%)	9 (26)		
Acute polymorphic psychotic disorder with symptoms of schizophrenia[b], no. (%)	26 (74)		
Education, years; mean (SD)	13.7 (1.9)	14.2 (1.8)	.32
Edinburgh Handedness Inventory score; mean (SD)	87.2 (13.2)	88.0 (10.8)	.82
PANSS Positive Subscale; mean (SD)	17.6 (7.5)		
PANSS Negative Subscale; mean (SD)	16.4 (4.8)		
PANSS General Psychopathology Subscale; mean (SD)	37.1 (10.4)		
PANSS total; mean (SD)	71.2 (19.0)		
[c]Duration of untreated psychosis (wk); mean (SD)	19.6 (16.6)		
Age at disease onset; mean (SD)	28.1 (6.8)		
Chlorpromazine equivalents, mg/d; mean (SD)	412 (186.5)		
Duration of antipsychotic treatment (wk); mean (SD)	9.9 (13.3)		

Note: FES, First-episode schizophrenia-spectrum patients; HC, healthy controls; PANSS, Positive and Negative Symptom Scale.
[a]Pearson's Chi-square test.
[b]The ICD 10 diagnosis of acute and transient psychotic disorders is congruent with DSM-IV defined brief psychotic disorder.
[c]Number of weeks between first psychotic symptoms and initiation of treatment.

retardation, a history of substance dependence and any MRI contraindications.

After description of the study, written informed consent was obtained from all participants. The protocol was approved by the institutional review boards of the Prague Psychiatric Center and Psychiatric Hospital Bohnice.

Task and Design

During fMRI, a SA experience was elicited and contrasted against OA perception in a motor task using manipulation of the degree of incongruence between the subject's motor intentions and the visual feedback.

A simple scene (figure 1A) was presented using Java-based software running on a computer connected to a LCD projector. Stimuli were projected onto a mirror attached to the head coil through a screen positioned at the head end of the scanner bore.

Participants were instructed to maintain steady movements of a cursor using a MRI-compatible joystick. They were told that occasionally they would not see their own movements, but instead they would observe cursor movement intrusions that looked like they were driven by the experimenter from outside of the scanner. In reality, software-based random angular distortions of subject's own actions were generated throughout OA blocks. This approach was necessitated due to differences in agency processing in human-human interaction compared to human-computer co-acting.[25] By use of this approach, we were able to manipulate the sense of agency at the onset of the corresponding SA/OA block.

During the OA block angular cursor movement was influenced by the software constantly. However, speed of cursor movement was dependent only on the velocity of joystick movements driven by examined subjects in both blocks (ie, OA and SA, see further below). Angular distortion in OA blocks were added to actual angle in polar coordinate system in a fixed manner depicted in figure 3. Despite usage of this fixed pattern of distortion, debriefing revealed no evidence for recognition of either exact regularity or artificiality of this approach. As intended, all participants attributed cursor movement deviations during OA to the other human subject.

The design alternated between 12 blocks of OA and 12 SA blocks with an absence of any visual-feedback distortion. Each block lasted 20 seconds.

Participants were blinded to the sequentiality and length of both SA and OA blocks. The blocks were presented in fixed alternating sequence. Post-experimental debriefing revealed no impact of this regular design on genuine experience of SA or OA.

Experimental subjects were instructed to keep moving the cursor either inside the central square if the movement they saw was subjectively interpreted as influenced by the "experimenter," or shift it promptly to the outer corridor as soon as they gained a distinct feeling of SA.

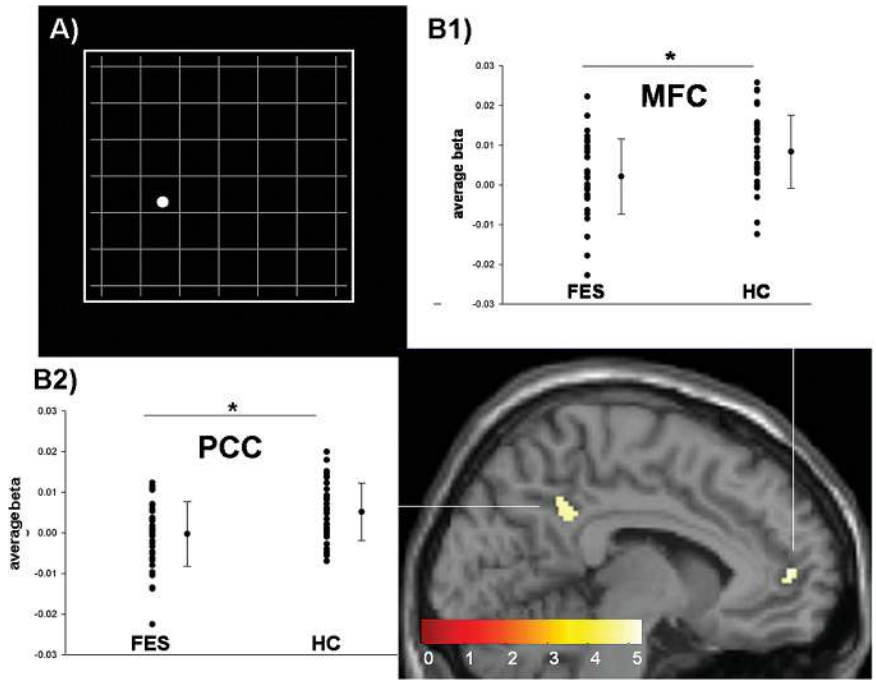

Fig. 1. A) Representative screenshot of self/other-agency judgment task used in the functional magnetic resonance imaging (fMRI). B1,2) Average beta values (mean, SD) of clusters that are different during self-agency judgment in HC > FES contrast. PCC, posterior cingulate cortex; MFC, mediofrontal cortex. *$P < .01$, t test. C) Whole-brain between-group analysis showing the regions that were significantly more active in the control group relative to the first-episode schizophrenia-spectrum (FES) group during self-agency judgment. Family-Wise Error (FWE) corrected, voxel level, $P < .05$. Color bar represents t values.

In such a case they were instructed to remain moving in this sector until the subjective onset of the next "experimenter's" intrusion. No movement cessation was allowed during the task. To ensure that participants fully understood the task prior, all subjects underwent 3-minute training period in the scanner.

Java-based software enabled us to record entire cursor track. This way we could confirm subsequently that all subjects enrolled in this study were compliant with the instructions. In addition, the software allowed for recording the exact coordinates of the cursor and thus track the cursor in real time. Therefore, target events (TEVS), when the cursor crossed the boundaries of the central square towards the outer corridor during a time-window encompassing the entire SA block, could be accurately determined. TEVS represented behavioral references to an emergent SA experience, which was the main interest of the study. Fixed OA onsets were initiated by software-driven shift of the cursor into the central square at the predefined start of all OA blocks.

In order to analyze BOLD correlates of an emergent SA/OA insight, in further analyses we used modified 10-second condition episodes with onsets cued either by individual TEVS (further in the text as "SA condition"), or beginning of OA block (further in the text as "OA condition"). TEVS detection allowed us to minimize potentially impaired overall performance.

Imaging Procedure

Imaging was performed on a 3 Tesla Siemens TRIO Tim scanner equipped with a standard 12-channel head coil. For the localization of the activated voxels and fMRI data preprocessing the subjects were scanned using a structural T1-weighted (T1W) 3D-MP-RAGE sequence with repetition time (TR) of 2300 ms, echo time (TE) 4.6 ms, bandwidth 130 Hz/pixel and with isotropic spatial resolution of $1 \times 1 \times 1\,mm^3$. Functional images sensitive to the BOLD contrast were measured with a gradient echo echo-planar sequence (GRE-EPI, TR = 2000 ms, TE = 30 ms, flip angle 90°, voxel size of $3 \times 3 \times 3$ mm, FOV = 192 mm × 192 mm, matrix size 64×64, each volume with 30 axial slices without an inter-slice gap, a total of 240 volumes). The data were preprocessed with SPM8 (Statistical Parametric Mapping; version 8, http://www.fil.ion.ucl.ac.uk) using realignment, spatial normalization into standard stereotactic space (EPI template; Montreal Neurologic Institute, MNI-152), and smoothing with a Gaussian kernel ($8 \times 8 \times 8\,mm^3$ full width at half maximum). Images and movement parameters were screened for potential movement artifacts prior to data analysis.

fMRI Analysis

fMRI data analysis performed in SPM8 comprised 4 stages:

1. The task-related BOLD response was assessed using finite impulse response (FIR) with the length of 10 seconds in all participants.[26] A General Linear Model was used to provide estimates of the signal changes at 6 time points shifted with an interval of 1 second since the onset of TEVS (having constant time window of 10 s), without making a priori assumptions about the shape of the HR. This approach enabled us to avoid errors associated with ill-fitting canonical models.[27] The beta estimates for the FIR models entered a second level analysis (Family-Wise Error [FWE] corrected, $P < .05$). A time bin 5 seconds after TEVS was chosen as the peak BOLD response occurred during this period for both groups pooled together. Identical 5-second delay after fixed OA block onset was arbitrarily used for the OA condition as well.
2. Individual first-level contrast images were generated for the SA and OA conditions respectively (FWE-corrected, $P < .05$). One-sample t test was performed to generate a within-group activation maps.
3. For the between-group analysis, 2-sample t test was performed at the whole brain level (FWE corrected voxel-wise, $P < .05$, minimal cluster size > 20 voxels). The anatomical localization was defined using the Talairach Daemon Atlas.[28]
4. A post hoc SPM8 multivariate regression analysis was conducted to determine the effect of psychopathology (PANSS) and chlorpromazine-equivalent antipsychotic-dosages on functional activation, respectively. The analysis was confined to a region of interest (ROI, the medal frontal cortex, the cingulate gyrus and the medial precuneus) encompassing areas that demonstrated significant between-group activation differences.

Task-Related ICA

A group spatial ICA was performed on fMRI data of all subjects during SA/OA judgment task using the GIFT toolbox (http://icatb.sourceforge.net). The number of independent components (ICs) to be extracted (after 3 Principal Component Analysis reduction steps) was estimated prior to ICA analysis using a modified minimum description length algorithm.[29] To test the robustness, an ICASSO analysis was performed,[30] based on 20 ICA iterations. ICASSO toolbox implemented in GIFT was used for investigating the algorithmic and statistical reliability of independent components by clustering and visualization. The method is based on running the ICA algorithm many times with slightly different conditions and visualizing the clustering structure of the obtained components in the signal space. The ICA algorithm produced ICs depicted as spatial maps and corresponding time-courses, both calibrated using z-scores. Spatial maps were thresholded at the $z > 3$. Anatomical labels were determined using the Talairach Daemon Atlas.[28]

Further, non-reliable components detected by means of ICASSO were removed. To exclude ICs containing artifacts outside the cortex, we computed spatial correlations between individual component maps and maps of prior probability of white matter or CSF as implemented in SPM8. The criteria for artifact detection were $r^2 > .05$ for correlations with CSF priors and $r^2 > .02$ for correlations with white matter priors.[31] To determine task-related ICs, we performed a regression analysis on the ICA with time-courses of SA and OA blocks. Consequently, 1-sample *t* test was performed to compare the mean beta weight against zero in each component and the corresponding SA/OA block, respectively.

For between-group comparisons of SA and OA component time-courses, a 2-sample *t* test was performed upon the beta weights from the regression analysis[32] with the level of significance at $P < .05$.

To further analyze functional network connectivity,[33] we analyzed the similarity of time courses of the signal between individual components related to SA and OA blocks, allowing for activity time lags between individual components. This approach modeled the temporal dynamics of the network's dependence.[33] We computed maximal parametric correlations between the component time-courses within a time interval of ±3 seconds in each subject. The group differences in the between-network correlations and time-lags were then tested using a 2-sample *t* test (level of significance $P < .05$, FDR corrected).

Statistical Analysis of Behavioral Measures

Between-group comparisons in response accuracy during SA/OA judgment were evaluated. This measure referred to the proportion of time spent in a proper segment of the visual scene during a corresponding block with and without distortion of visual feedback.

In a second analysis we evaluated the difference in the number of TEVS initiating SA conditions that entered the final fMRI analysis.

Whereas the first variable objectively reflected overall performance, the second measure served as a subjective indicator of the SA/OA experience in which BOLD signal changes were subsequently calculated.

Between-group differences were analyzed by means of unpaired 2-tailed Student's *t* test, $P < .05$.

Results

Behavioral Performance

HC showed significantly higher overall response accuracy compared to FES (HC: mean 84.6, SD 5.9, FES: mean 65.9, SD 16.8; $t = 2.83$, $P = .006$). There was no statistically significant correlation between the PANSS (positive, negative, general psychopathology and total) score and overall response accuracy.

There was a similar number of TEVS in FES (mean 11.9, SD 0.2) and HC (mean 12.0, SD 0.2; $t = 0.58$, $P = .6$).

Between-Group Differences During the SA Condition

During the SA condition HC showed greater activation than FES in 2 significant clusters (table 2, figure 2C) located in the anterior portion of the CMS within the left medial frontal gyrus (BA 10) and the posterior part in the posterior cingulate gyrus (BA 31), respectively (FWE-corrected /voxel-level/, $P < .05$). There were no regions in which FES showed greater activation than HC.

Between-Group Differences During the OA Condition

There were no differences in activation/deactivation between the groups during OA experience.

Within-group effects of the SA/OA judgment are summarized in supplementary eTables 1 and 2.

Relationship of PANSS and Medication to fMRI Activity

There were no associations between the task-related activation and potential confounds (antipsychotic dose expressed as chlorpromazine equivalent or PANSS positive, negative, general psychopathology and total scores) within ROI consisting of CMS (FWE corrected, $P < .05$).

Task-Related ICA

A minimum description length algorithm extracted 35 task-related ICs in total. Out of these, 12 components were excluded from further analysis; 8 components were determined as nonreliable using the ICASSO algorithm (stability index below 0.9), 3 components showed high spatial correlations with CSF maps, and 1 component correlated with the WM map.

Task-related ICA revealed 3 ICs (C2, C9, C23) specifically associated with the time course of SA/OA blocks

Table 2. Results of Between-Group Analysis for Contrast Between Self-Agency Experience and Other-Agency

Cluster Size	*t* Value	Talairach Coordinates			Hemisphere	Region
		x	*y*	*z*		
168	5.4	−4	51	2	Left	Medial frontal gyrus; BA 10
40	5.0	−8	−32	36	Left	Posterior cingulate gyrus; BA 31

Note: BA, Brodmann Area. Healthy Controls > FES. Whole brain analysis, FWE (Family-Wise Error) correction of *P* value ≤ .05 with a minimum cluster consisting of >20 voxels.

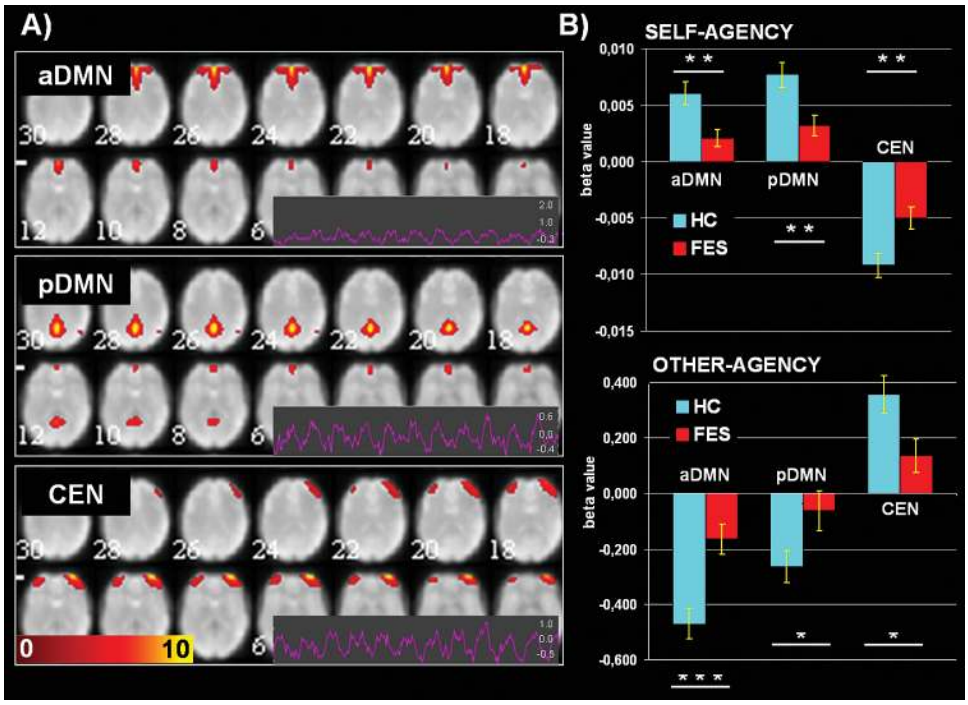

Fig. 2. A) A spatial maps of 3 task-related independent components (IC) based on regression analysis of the independent component analysis (ICA) with time-courses of the self/other-agency conditions. The maps and time courses were identified by GIFT software and correspond to the mean component estimates of all 70 subjects (FES patients and healthy control subjects). aDMN, anterior part of default mode network; pDMN, posterior part of DMN; CEN, central executive network. The connectivity *Z* scores, values ranging from 0 to 10, are displayed in red-to-yellow (see color scale at bottom left). The bottom right plots depicts the mean time course averaged across subjects of the corresponding IC scaled to *z*-scores. B) Average beta values (with SE) for corresponding aDMN, pDMN and CEN components. Blue bars represent healthy controls (HC), red bars depict the first-episode schizophrenia-spectrum patients (FES). Positive beta values indicate activation, whereas negative beta values index deactivation. **P* < .05, ***P* < .01, ****P* < .001, *t* test.

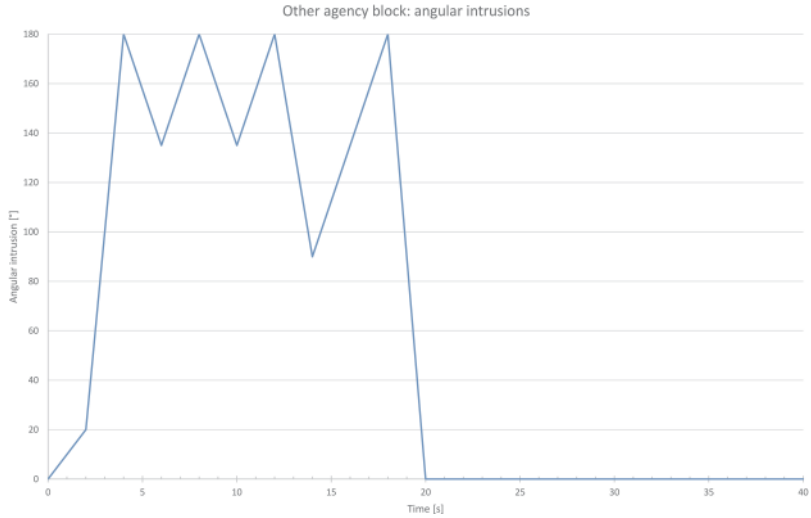

Fig. 3. Angular instrusions introduced during other-agency (OA) blocks.

in a pooled-sample analysis (figure 2A, table 3). Whereas C9 represented mainly the posterior part of the DMN (pDMN, posterior cingulate, precuneus) C2 mapped predominantly onto the anterior portion of the DMN (aDMN) with intrinsic activity prevailing in the medial frontal gyrus extending to the most rostral parts of the anterior cingulate and superior frontal gyrus.[34,35] The C23 component, encompassing the superior, middle and inferior frontal gyrus bilaterally, was identified as the central-executive network (CEN).[36]

Table 3. Task-Related ICA: Independent Components Corresponding to Self/Other-Agency Judgment in a Pooled Sample of FES and HC (n = 70)

Region	Volume (cm^3) of Left/Right	Random Effects: Max Value (x, y, z) Left/Right[a]
aDMN (C2)		
Medial frontal gyrus; BA 9,10	3.8/3.8	9.2 (0, 46, 20)/8.3 (4, 55, 17)
Anterior cingulate; BA 10, 24, 32, 33	2.5/2.4	7.3 (0, 38, 20)/6.0 (4, 40, 16)
Superior frontal gyrus; BA 9, 10	4.8/5.7	7.1 (−4, 56, 25)/7.3 (4, 56, 25)
Middle frontal gyrus; BA 10	0.6/0.6	5.6 (−22, 55, 21)/5.3 (24, 55, 21)
Cingulate gyrus; BA 32	0.6/0.4	4.9 (−4, 36, 26)/4.6 (4, 29, 26)
pDMN (C9)		
Posterior cingulate; BA 23, 29, 30, 31	3.4/3.5	7.9 (0, −51, 21)/7.5 (4, −51, 25)
Cingulate gyrus; BA 23, 31	3.4/2.8	7.9 (0, −55, 27)/7.3 (4, −51, 28)
Precuneus; BA 7, 23, 31	4.7/3.8	7.5 (0, −55, 30)/6.9 (4, −55, 30)
Cuneus; BA 7	0.1/0.1	4.9 (0, −66, 33)/4.3 (4, −66, 33)
Medial frontal gyrus; BA 10	0.6/0.4	4.8 (−4, 50, −3)/4.2 (4, 50, −4)
Anterior cingulate; BA 10, 32	0.1/0.3	4.1 (−4, 47, −2)/4.3 (4, 52, −1)
CEN (C23)		
Middle frontal gyrus; BA 10, 46	3.8/9.0	4.9 (−32, 55, 6)/9.1 (32, 58, 4)
Superior frontal gyrus; BA 10	0.6/3.4	3.9 (−32, 54, −1)/8.3 (28, 58, 4)
Inferior frontal gyrus; BA 10, 46	0.4/2.5	3.8 (−44, 43, 9)/6.7 (42, 52, 1)

Note: ICA, independent component analysis.
[a]The components Talairach coordinates and respective degree of activation in clusters defined.

Task-Related ICA in the SA Blocks

In a pooled sample, there was a positive association of aDMN and pDMN with the time course of SA blocks (mean beta weight in aDMN against 0: $t = 5.8$, $P < .0000001$, pDMN $t = 6.9$, $P < .0000001$). Conversely, there was a negative association of CEN with the time course of SA blocks (mean beta weight against 0: $t = -9.05$, $P < .0000001$).

FES and HC showed significant between-group differences in beta-weights obtained from regression analysis between component time-courses and the SA blocks. Beta-weights for both aDMN and pDMN were significantly reduced in FES compared to HC ($t = 3.129$, $P = .0026$ for aDMN and $t = 3.197$, $P = .002$ for pDMN, respectively) indicating a decreased activation of these networks during the SA blocks in patients. Moreover, FES subjects had higher beta-weights for CEN ($t = -2.798$, $P = .0067$) suggesting impairment in CEN deactivation during the SA experience (figure 2B).

Task-Related ICA in the OA Blocks

During the OA blocks, pooled-sample analysis showed a significant association in the time-courses of the aDMN, pDMN and CEN, however, in a completely reversed manner. CEN showed positive, whereas aDMN and pDMN exhibited negative association with time course of OA blocks, respectively (mean beta weight against 0 in aDMN: $t = -6.5$, $P < .0000001$, pDMN: $t = -3.49$, $P = .0008$, CEN: $t = 5.33$, $P = .000001$).

CEN beta-weights were significantly reduced in FES in comparison to HC ($t = 2.473$, $P = .016$), indicating decreased network activation during the OA blocks. Concurrently, FES showed higher aDMN and pDMN beta-weights during the OA blocks in comparison to HC ($t = -3.979$, $P = .0002$ for aDMN and $t = -2.212$, $P = .03$ for pDMN), suggesting impaired aDMN/pDMN deactivation during the OA experience in patients (figure 2B).

Functional Network Connectivity

Functional network analysis was performed on the 3 components selected from previous analysis: aDMN, pDMN and CEN. There was a reduced positive correlation between aDMN and pDMN in FES compared to HC ($t = 3.02$, $P = .0035$) during time courses of SA/OA blocks. Conversely, patients exhibited higher positive correlation between aDMN and CEN ($t = -4.223$, $P = .00007$). Both groups showed negative correlations between the pDMN and CEN networks, however, no between-group differences were found in this variable.

Discussion

The most important finding of the present study was that even with the use of a self-paced fMRI design that minimized performance confounds, the FES group exhibited a deficit in cortical activation during the emergent SA experience within the CMS, which is normally involved in SA processing.[13–16] This yielded significant between-group differences in activation during SA recognition.

A second major finding was that according to the ICA analysis, 2 major brain networks, DMN and CEN, were

specifically correlated with time-courses of SA/OA blocks and this mechanism was compromised in FES.

To our knowledge, this is the first study to demonstrate that DMN is positively and CEN negatively associated with the SA judgment, whereas the OA judgment exhibits a complete reversal of the above. Therefore, the judgment of agency task used in this study showed to be particularly suitable for exploring task-dependent dynamics of major large-scale brain networks within a single activation paradigm.

It is widely accepted that DMN exhibits spontaneous correlation during the resting state[37] and shows increased activity during internally directed cognitive processes.[15,38] Conversely, in previous literature, CEN has been reported to be specifically implicated in processing of external stimuli to enable task performance.[39]

Our findings expand the previous investigations to show that DMN/CEN antagonistic activity is a key component not only of the attention-demanding task vs rest switching, as previously suggested in literature, but also of the SA/OA judgment dichotomy.

In this study a significant impairment of this mechanism was detected in FES individuals. First, according to task-related ICA, FES showed decreased DMN activation and reduced CEN deactivation during the SA and a reversal of this finding during the OA judgment, respectively, in comparison to HC (figure 2B). Second, we found a globally higher positive correlation between otherwise anti-correlated activity of DMN/CEN during SA/OA judgment in FES vs HC.

These findings correspond to a wealth of studies showing that disrupted functional connectivity within and between the DMN and CEN is one of the most prominent findings in the disease.[40–47] An impaired machinery of DMN/CEN dynamics in schizophrenia suggests that the main site of pathology may originate in higher-order regulatory mechanisms.[46,48,49]

The specificity of above-mentioned findings for self-related psychological symptoms is unclear. At the same time, disrupting activity in the medial prefrontal cortex by deep transcranial magnetic stimulation lowered self-awareness and induced feelings of dissociation.[50]

A key question remains, whether the deficient CMS recruitment contributes to also an aberrant sense of agency in patients that is expectedly pronounced as positive, and in particular first-rank symptoms of the disease.[51] On a behavioral level, when performing the task inside a scanner, patients showed a significantly lower response accuracy compared to controls, supporting an evidence of overall impairment in SA/OA judgment in schizophrenia-spectrum disorders.[52] Interestingly, there was no association between a deficit recruitment of CMS and symptom severity measured by PANSS, which has been reported previously.[43,53–55] This could be related to relatively narrow range of illness severity and the selection of patients at or near the onset of remission. Alternatively, a self-monitoring deficit was also detectable in unaffected siblings of patients with schizophrenia,[10] and therefore may rather represent specific endophenotype within the schizophrenia spectrum. Thus, further examination of neural correlates during SA/OA judgment task in clinically unaffected relatives of schizophrenia patients and high-risk subjects would be warranted.

Additionally, our findings showed reduced functional connectivity between pDMN and aDMN in FES compared to HC. This is in line with previous reports of decoupling between midline hubs of DMN.[56–58] Also higher positive correlation between CEN and DMN in patients when compared to controls identified in this study corresponds to previous findings.[43,59,60] These results indicate a complex nature of both within- and between-network DMN/CEN dysconnectivity in schizophrenia.

One of the strengths of the current study is the inclusion of only FES patients. In this sense, the patient group was homogenous, and avoided several possible confounding factors associated with illness chronicity, age, and prior long-term exposure to antipsychotic medication.

However, several limitations are noteworthy. First, despite the use of fMRI design based on subject's individual reports of SA, we cannot fully rule out involvement of performance-related confounds that generally bias case-control studies in schizophrenia. Nevertheless, we observed a similar pattern of intra-group deactivations during OA condition and identical neural correlate of OA condition in both FES and HC (supplementary eTables 1 and 2). This suggests at least an equal allocation of cognitive effort in both studied groups. Second, a relatively small sample size increases the risk of type II errors. These limitations may have effect on fMRI variables presented herein and thus results should be taken as indicative rather than absolute.

Studying the mechanisms by which opposing DMN/CEN dynamics may drive self/other discriminative processes holds promise for a better understanding of the phenomenology of schizophrenia.

Supplementary Material

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

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