Psychiatry Research: Neuroimaging 324 (2022) 111495

Contents lists available at ScienceDirect

Psychiatry Research: Neuroimaging

journal homepage: www.elsevier.com/locate/psychresns

Articles

Default mode network components and its relationship with anomalous self-experiences in schizophrenia: A rs-fMRI exploratory study

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A R T I C L E I N F O

Keywords:
Anterior cingulate cortex
Functional magnetic resonance imaging
Metacognition
Parahippocampal gyrus
Psychosis

A B S T R A C T

Anomalous self-experiences (ASEs) in schizophrenia have been under research for the last 20 years. However, no neuroimage studies have provided insight of the possible biological underpinning of ASEs. In this novel approach, the connectivity within the default mode network, calculated through a ROI-based analysis of functional magnetic resonance imaging data, was correlated to the ASEs scores assessed by the Inventory of Psychotic-Like Anomalous Self-Experiences (IPASE) in a sample of 22 schizophrenia patients. The Pearson's correlation coefficients between IPASE scores and intrahemispheric connectivity of the parahippocampal gyrus with the isthmus cingulate cortex in both hemispheres, and right parahippocampal gyrus with the right rostral anterior cingulate cortex were positive and significant suggesting a relation between hyperactive functional connectivity and anomalous self-experiences intensity. Prior literature reported these areas to have a role in self-processing and consciousness as well as being anatomically connected. Further research with larger sample size and comparison with controls are needed to confirm the relationship of this connectivity with anomalous self-experiences.

1. Introduction

Over the last 20 years, research has raised attention on the anomalous self-experiences (ASEs) as a core trait of psychosis (Sass and Parnas, 2003; Uhlhaas and Mishara, 2007). Such experiences are disturbances in the subjective experience of the self and are common in schizophrenia patients (Parnas and Handest, 2003). The main way to assess ASEs is the use of phenomenological and clinical instruments like the semi-structured phenomenological interview Examination of Anomalous Self-Experiences (EASE) (Parnas et al., 2005) or the more recently validated Inventory of Psychotic-Like Anomalous Self-Experiences (Cicero et al., 2017). The research on ASEs has focus on its relationship with cognitive deficits and positive/negative symptoms in schizophrenia (Cicero et al., 2016; Hernández-García et al., 2021; Trask et al., 2021). These studies have found that ASEs are related to emotion processing deficits (Cicero et al., 2016), motor speed and solving problems performance (Hernández-García et al., 2021) and attention, visual learning, reasoning, and working memory (Trask et al., 2021). In addition, ASEs have been found to have similar levels in the schizophrenia spectrum (i.e. schizophrenia, schizoaffective disorder, and schizophreniform disorder) (Haug et al., 2012; Nordgaard and Parnas, 2014), and that it is significantly lower in other psychotic conditions like bipolar psychosis (Haug et al., 2012).

More broadly speaking, the self and subjective experience of oneself have been widely studied in psychology and psychiatry (Gusnard et al., 2001; Lane, 2020; Mishara, 2007; Northoff et al., 2011; Northoff and Hayes, 2011; Qin et al., 2020). Contrary to ASEs, the neural correlates of the self have been studied using neuroimage (Gusnard et al., 2001; Northoff et al., 2011), mainly through the study of consciousness and its disorders (former vegetative state) (Crone et al., 2011; Långsjö et al., 2012; Qin et al., 2010), in addition to phenomenology (Lane, 2020; Mishara, 2007; Parnas and Handest, 2003; Zhao et al., 2013). One of the brain areas of interest in self studies is the default mode network (DMN) (Crone et al., 2011; Mishara, 2007; Vanhaudenhuyse et al., 2010). Although its boundaries are still in debate (Buckner and DiNicola, 2019), the DMN includes the isthmus cingulate gyrus (iCC), the

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https://doi.org/10.1016/j.pscychresns.2022.111495
Received 30 November 2021; Received in revised form 28 April 2022; Accepted 22 May 2022
Available online 24 May 2022
0925-4927/

posterior cingulate gyrus (PCC), the precuneus cortex (PCUN), the rostral anterior cingulate cortex (rACC), and the parahippocampal gyrus (paraH) (Andrews-Hanna et al., 2010; Buckner et al., 2008; Buckner and DiNicola, 2019; Kabbara et al., 2017). As DMN is active during resting state, it is associated with attention to internal stimuli and self-referential processing (Buckner et al., 2008; van Buuren et al., 2012). There is also research in which, although the DMN as a whole was not the matter of study, DMN components are highlighted as relevant, like the ACC in impaired consciousness (Långsjö et al., 2012; Qin et al., 2010) or the PCC in self-referential tasks (Denny et al., 2012). As DMN and its components are of interest for the healthy self and both healthy and impaired consciousness, it is therefore a relevant starting point for the study of the impaired or altered self in schizophrenia. In fact, integration of phenomenology and neuroscience is the main challenge and future direction on ASEs (Borda and Sass, 2015; Sass, 2014).

The aim of this exploratory study is to preliminary explore the relation between DMN function and ASEs in schizophrenia. Therefore, we calculated the correlations coefficients between ASEs, assessed with the IPASE, and the connectivity between the components of the DMN.

2. Materials and methods

Our sample included 22 patients, 10 with chronic schizophrenia and 12 with first episode of schizophrenia. Patients were diagnosed by one of the experienced psychiatrists in the group (OMS and VM) according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders 5th edition, taking into account current mental state, clinical records and relatives' information.

Exclusion criteria were (a) intelligence quotient under 70; (b) present or past substance dependence (excluding caffeine and nicotine); (c) head trauma with loss of consciousness; (d) neurological or mental diagnosis different to schizophrenia; (e) any other treatment affecting central nervous system. All participants provided written informed consent after full written information. The local ethics committee endorsed the study. This work complies with the ethical standards of the Helsinki Declaration of 1975, as revised in 2008. Previous work of our work used the IPASE data of this sample within a wider sample of patients (Hernández-García et al., 2021), while the fMRI data has not been used elsewhere. The socio-demographic and clinical characteristics are presented in detail in Table 1.

2.1. Materials and methods

High resolution 3D T1-weighted MRI data were acquired using a Philips Achieva 3T MRI unit (Philips Healthcare, Best, The Netherlands) with a 32-channel head. For the anatomical T1-weighted images, acquisition parameters were: Turbo Field Echo (TFE) sequence, repetition time (TR) = 8.1 ms, echo time (TE) = 3.7 ms, flip angle = 8°, 256 × 256 matrix size, 1 × 1 × 1 mm^3 of spatial resolution and 160 slices covering the whole brain.

Table 1
Sociodemographic and clinical characteristics of the sample.

	Ratio	Minimum	Maximum	Mean	Standard Deviation
Sex (M:F)	9:13	-	-	-	-
Age (years)	-	20	55	33.63	11.26
Educational level (years)		8	18	12.61	3.18
Illness duration (months)	-	0	321	58.54	95
Diagnoses (S:FE)	10:12	-	-	-	-
CPZ equivalents (mg)	-	100	1225	360.9	242.84
PANSS positive	-	7	20	12.05	3.39
PANSS negative	-	7	36	15.27	6.49
PANSS totals	-	31	84	49.59	13.49

M: Male, F: Female, S: Schizophrenia, FE: First Episode.

Table 2
Partial correlation between IPASE scores and functional connectivity in pairs of components for the right hemisphere controlled for PANSS scores and age.

Right-DMN components	r-rACC	r-iCC	r-paraH	r-pCC	r-pCUN
r-rACC		.411	.616**	-.241	.290
r-iCC			.604**	-.247	0.95
r-paraH				.378	.443*
r-pCC					-.236
r-pCUN					

The values on the diagonal do not provide information and therefore they have been removed. As a symmetric matrix, the off-diagonal values are mirrored. Repeated values on the down/left side of the table have been removed. r-: right, rACC: rostrar anterior cingulate cortex, iCC isthmus cingulate gyrus, paraH: parahippocampal gyrus, pCC: posterior cingulate gyrus and pCUN: precuneus cortex.
* $p < 0.05$, ** $p < 0.01$

Table 3
Partial correlation between IPASE scores and functional connectivity in pairs of components for the left hemisphere controlled for PANSS scores and age.

Left-DMN components	l-rACC	l-iCC	l-paraH	l-pCC	l-pCUN
l-rACC		.041	.311	-.295	-.101
l-iCC			.445*	-.022	.031
l-paraH				.406	.207
l-pCC					-.095
l-pCUN					

The values on the diagonal do not provide information and therefore they have been removed. As a symmetric matrix, the off-diagonal values are mirrored. Repeated values on the down/left side of the table have been removed. l-: left, rACC: rostrar anterior cingulate cortex, iCC isthmus cingulate gyrus, paraH: parahippocampal gyrus, pCC: posterior cingulate gyrus and pCUN: precuneus cortex. * $p < 0.05$

Rs-fMRI were acquired using TR = 3000 ms, TE = 30 ms, flip angle = 80°, 80 × 80 matrix size, 3 × 3 × 4 mm^3 of spatial resolution, 35 axial slices covering the whole brain and 197 different volumes. During this acquisition, the subject was ordered to close the eyes without sleeping.

All the scans were acquired during the same session, starting with the T1-weighted scan, followed by the diffusion-weighted scan (which is not used in this study) and ending with the rs-fMRI scan. Total acquisition time for each subject was approximately 28 min, divided in the following periods of time: six minutes for the T1-weighted scan, 12 min for the dMRI scan, and 10 min for the rs-fMRI scan.

2.2. Image preprocessing and analysis

With respect to the rs-fMRI data, some preprocessing steps were firstly applied. These steps were motion correction, outlier detection, coregistration to the T1-weighted image, structural segmentation and denoising. The denoising step was carried out with a band-pass filter using 0.01 and 0.1 Hz as cutoff frequencies.

The functional connectivity was evaluated with the correction values of the Blood-oxygen-level-dependent (BOLD) signal, i.e., the signal provided by the fMRI data. We defined the correlation values as the Pearson's correlation values between the BOLD signal samples of the regions of the DMN. Considering the limited range of values of the Pearson's r value, between -1 and 1, we employed the Fisher r-to-*Z* transformation to overcome this restriction and define the correlation values as *Z*-scores. To define the regions of the DMN, five regions included in the Desikan-Killiany atlas were chosen according to a previous studies (Andrews-Hanna et al., 2010; Buckner et al., 2008; Buckner and DiNicola, 2019; Desikan et al., 2016; Kabbara et al., 2017): iCC, PCC, PCUN, rACC, and paraH. Considering these regions, we organized the correlation values in two 5 × 5 symmetric connectivity matrices, one for each hemisphere, where each row and its corresponding column represent a particular region, and each cell contains a connectivity value between two regions. The values of the main diagonal were excluded (auto-correlation values). Therefore, 20 unique connectivity values were used in this assessment. The whole rs-fMRI pipeline was carried out using the CONN software, v.17(Whitfield-Gabrieli and Nieto-Castanon, 2012), run under MATLAB version 2020a.

2.3. ASEs

ASEs were scored using the Inventory of Psychotic-Like Anomalous Self-Experiences (IPASE) (Cicero et al., 2017). The IPASE is a 57-item self-report scale in which participants, in the presence of the researcher, indicate how much they agree with statements on a Likert scale of 1 (Strongly Disagree) to 5 (Strongly Agree). The inventory was completed by the patients in the presence of the same experienced psychiatrist to avoid external bias. A factorial structure is used in IPASE and, therefore, it can be subdivided in 5 subscales: cognitive (7 items), self-awareness and presence (22 items), consciousness (6 items), somatization (17 items) and demarcation/transitivism (5 items). According to the statistical analysis performed in the validation of the inventory (Cicero et al., 2016), it is appropriate to sum the subscales score to a single IPASE score. Thus, to avoid an inflation of comparisons we only used for our correlative analyses this total score.

2.4. Statistical analysis

The functional connectivity values employed in the present study were the *Z*-scores, which were extracted with the r-to-Z Fisher transformation. To determine the potential relationship between the functional connectivity and the IPASE scores, the Pearson's correlation was calculated between the *Z*-score from each connection from the DMN and the total score from the IPASE scale. To address the possible effect of age and PANSS scores, partial correlation was carried out controlled for these two variables. Before the partial correlation analysis, to take into account the possible effect of illness stage (first episodes vs. chronic), *t*-test were applied for all brain connectivity values, IPASE scores and PANSS scores. No significant differences between the two groups were found. This was carried out with SPSS (Statistics IBM Corp. Released 2019. IBM SPSS Statistics for Windows, Version 26.0. Armonk, NY: IBM Corp). The threshold for statistical significance was set at $p<0.05$. A database with the main data supporting the present results is available (Mendeley Data doi: 10.17632/gnm55447gv.1).

3. Results

The results of the correlation between functional connectivity and IPASE scores can be seen in tables 2, for the right hemisphere, and 3, for the left hemisphere. Three significant correlations with ASEs scores were found in the right hemisphere, all of them positive and involving the paraH. One positive significant correlation with ASEs was also found in the left hemisphere, involving the paraH.

Regarding the correlation between right-paraH-pCUN connectivity and IPASE scores, a post hoc descriptive analysis of the significance correlations showed how this correlation was highly influenced by an outlier. The removal of this outlier increases the *p*-value up to 0.088. The scatter plot of the strongest partial correlation can be seen in Fig. 1. The cortices which connectivity had a significant correlation with IPASE scores, excluding the spurious PCUN correlation, are shown in Fig. 2.

4. Discussion

To the best of our knowledge, this study is the first one addressing the biological underpinnings of the ASEs. Our results support its relation to a higher connectivity of the paraH in both hemispheres. The paraH, besides its function in memory (Aminoff et al., 2007, 2013; Hayes et al., 2007; Li et al., 2016) has been also associated with mayor activity in

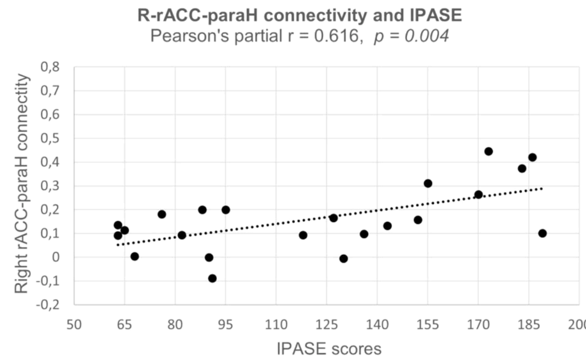

Fig.1. Scatter plot for the connectivity between the right rostral anterior cingulate cortex (rACC) and parahippocampal gyrus (paraH) in the vertical axis (*Z*-scores) and the IPASE scores in the horizontal axis.

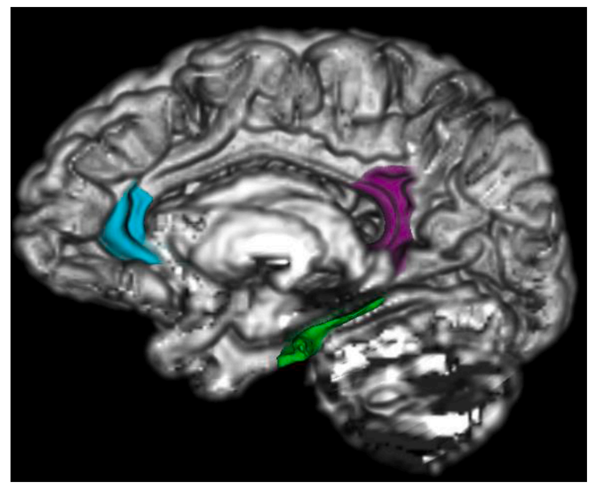

Fig.2. Desikan-Killiany atlas areas corresponding to the parahippocampal gyrus (green), the isthmus cingulate gyrus (purple) and the rostral anterior cingulate cortex (light blue).

self-evaluation in comparison with other-evaluation (Schmitz et al., 2004; Yoshimura et al., 2009). In (Yoshimura et al., 2009), the authors hypothesize that this activation may be linked to the role of autobiographical memory in self-evaluation.

Regarding the ACC and the iCC, there is prior and extensively literature that attribute an important role of these cortices in the self. The activity in the ACC has been correlated with the level of consciousness in healthy subjects (Långsjö et al., 2012) under anaesthesia and in patients with consciousness disorder (Qin et al., 2010). In (Qin et al., 2010) the ACC showed increased activity in both patients and controls when self-related stimuli were presented, although the latter showed lower activity. In addition, the medial prefrontal cortex (mPFC), which overlaps almost completely with the rACC in the Desikan-Killiany atlas, has been widely reported to take part in self-referential thinking (Marques et al., 2019). In addition, it has been reported to be involved in judgements about the self and others (Gusnard et al., 2001; Zhao et al., 2013).

The iCC corresponds to the most posterior area of the cingulate cortex. In fact, the subdivision in PCC and iCC is not performed in other widespread atlases for cortical labelling like the Harvard-Oxford cortical structural atlas (Frazier et al., 2005; Goldstein et al., 2007; Makris et al., 2006) or the automated anatomical labelling atlas (AAL) (Tzourio-Mazoyer et al., 2002). The PCC has been also related with self-processing (Denny et al., 2012; van der Meer et al., 2010).

Furthermore, these three cortices are anatomically connected through the cingulate bundle (Huang et al., 2021; Sampath et al., 2017; Whitford et al., 2014). As these areas have been widely involved in the healthy self, and they are anatomically connected, a joint high activity within these areas is congruent with an altered self in schizophrenia (i.e ASEs).

The correlation between IPASE and connectivity in these areas is positive, higher the connectivity, higher the ASEs. Previous work of our group has found increased connectivity in the whole brain network in patients, measured by graph theory value connectivity strength over EEG data (Cea-Cañas et al., 2020; Gómez-Pilar et al., 2018). Higher connectivity strength has been also found in fMRI studies within patients in self- and other-reflection task (Ćurčić-Blake et al., 2015). In (Ćurčić-Blake et al., 2015) the aim of the study was to address the connectivity within self-related brain areas during task-fMRI and then correlate it with the insight patients have of their own disease. Among the results, a negative correlation was found between insight and connectivity of the PCC with the dorsal mPFC (poorer insight, higher connectivity). A pattern of higher connectivity associated with poor insight of one's disease (Ćurčić-Blake et al., 2015) and cognitive deficits (Cea-Cañas et al., 2020) in schizophrenia is in the line of the results of higher connectivity and impaired self in schizophrenia.

Regarding the limitations of the present study, the first one is the small sample size. The second limitation comes from the methodological approach. In order to avoid the spurious correlation effect between mirroring ROIs, as well as an inflation of comparisons the connectivity between components were performed within the hemispheres, although some research have found evidence of ipsilateral aberrant connectivity in schizophrenia (Meyer-Lindenberg et al., 2005). Therefore, the implication of interhemispheric DMN connectivity in ASEs is not explored in this study. Third, a large number of correlation analyses have been performed and the associated results were not corrected for multiple comparisons, increasing the probability of type I error. Multiple comparisons correction avoids the increase of type I error but increases the probability of type II error. Given the small simple size alongside with the novelty of the study and its exploratory nature according to a defined a priori hypothesis, avoidance of type II error should not be underestimated. Thus, we have considered that corrected non-significant results would be far less enlightening for the field of ASEs. Therefore, results on how parahippocampal connectivity is related to ASEs should be interpreted as a starting point for further research, not as solid evidence. Fourth, another limitation in the interpretation of the results, which is shared by most of the literature in neuroimage, is the presence of different atlases for the grey matter labelling. Some areas, like the iCC/PCC or the ACC/mPFC, are presence or absence depending on the atlas used, and perfect concordance between those that are common is unusual. Consequently, literature comparison is more challenging. Therefore, slightly misleading assumptions of perfect equivalence between different atlases are done. Fifth, the sample for this study is homogeneous, so there are no groups to make comparisons with. Further studies including healthy subjects, as well as other psychotic disorders are needed. Finally, the pCUN-paraH connectivity in this study is due to the presence of an outlier. Nevertheless, as the pCUN has been strongly related to consciousness (Cavanna, 2007), further research is needed to address if it is also related to ASEs.

This study constitutes a first step to address the biological underpinnings of the ASEs in schizophrenia. The results are congruent with the literature that have reported higher brain connectivity in schizophrenia associated with poorer insight, as well as the implication of the paraH, the ACC and the iCC in the healthy self and in both the healthy and impaired consciousness.

Author contributors

A. Roig, I. Fernández-Linsenbarth wrote the draft; M. Hernández-García and V. Molina, recruited patients; M. Hernández-García, R. Beño-Ruiz-de-la-Sierra and V. Molina collected clinical data and IPASE scores; A. Roig, R. de Luis and A. Planchuelo-Gómez analysed the data; V. Molina designed the study.

Declaration of Competing Interest

The authors declare no conflict of interest.

Acknowledgments

This work was supported by the following grants: "Instituto de Salud Carlos III" (grant ID PI18/00178), "Gerencia Regional de Salud de Castilla y León" (grant ID GRS 2121/A/20), and by predoctoral grants from the "Consejería de Educación - Junta de Castilla y León" and the European Social Fund (grant IDs VA-183-18 to IFL, VA-223-19 to RMBR) and by the postdoctoral grant from the European Union (NextGenerationEU to ÁGP).

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