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Research Article

Cross-Validation of Paranoid and Depressive Scales: Results From Functional MRI Group Independent Component Analysis

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Objective: Based on earlier research, we hypothesized that patient response to diagnostically relevant items (paranoid (DP) and depressive (DS)) from clinical self-assessment scale (PD-S) could be cross-validated when performed simultaneously with task-based fMRI, resulting in specific and common neural circuit activations in response to the PDS items. In the current study, we tried to overcome one of the limitations of our previous research, namely, the lack of a healthy control (HC) group. Thus, our aim was to investigate the possible differences between patients with schizophrenia (SCZ) and depression and HCs using independent component analysis.
Methods: A total of 72 subjects participated in this study, including 21 HCs, 26 patients with SCZ, and 25 patients with major depressive episode (DEP). Patients were scanned on a 3T MRI system using a functional MRI task representing statements from DP-DS scale and diagnostically neutral (DN) statements. The data were processed using group independent component analysis for fMRI toolbox (GIFT).
Results: Five components were identified as task-related, but only three of them were found to demonstrate statistical difference between SCZ, DEP, and HC, namely, components 6, 7, and 9. The contrast between SCZ and HC was presented by Component 6 (cingulate gyrus and basal ganglia), which exhibited significant difference when comparing all three active conditions. On the other hand, SCZ and DEP group differences were presented by Component 7 for DS-DN comparison (frontoparietal network and superior temporal gyrus) and Component 9 (medial frontal gyrus, precuneus, angular gyrus, and among others) which highlighted preferential processing related to the DP-DN and the DS-DP comparison.
Conclusion: Our results demonstrate differences in brain circuits processing preferentially diagnostic stimuli across the three groups. Those circuits involve mainly networks of cognitive and affective functioning, which provides insights in their role for pathophysiology of SCZ and DEP. This evidence fosters the theory of transdisciplinary validation, where neurobiological measure such as functional MRI is determined as external validity operation for the diagnostic assessment scales. This can facilitate the use of clinical evaluation methods as proxy measures of brain functions.

Keywords: clinical self-evaluation scales; depression; functional MRI; group independent component analysis; schizophrenia

1. Introduction

Schizophrenia (SCZ) and depression (major depressive episode (DEP)) are debilitating mental illnesses characterized by a complex interplay of biological, psychological, and environmental factors. These disorders often result in significant functional impairments and increased morbidity and mortality and impose a substantial economic burden on society [1, 2].

Diagnostic precision of SCZ and DEP remains a challenge due to a lack of consensus on the underlying etiological and pathophysiological mechanisms, hindering clinical assessment and treatment planning [3]. This has been a persistent and controversial topic in the field of psychiatry—a medical specialty, expected to be based on scientific evidence and approach backed by objective data and biomarkers as other medical fields are— but in reality, at the core of the diagnostic process, subjective clinical scales and interviews are to be seen. This leads to the diagnosis being influenced by both subjective patient–reported symptoms and clinician interpretation [4, 5]. Because of the nature of psychiatric illnesses, patient reports are crucial as they are the main presentation of the disorders; therefore, a translational method addressing the gap between the nomothetic and idiographic approach could be a promising strategy to confront the complexity of this issue [6].

Translational cross-validation of clinical self-rating scales (von Zerssen's paranoid depressive scale (PDS)) [7] and fMRI is a novel approach addressing this topic [8]. The clinical assessment tools are indeed not standard line for diagnostic evaluation, especially when compared to the self-assessment tests such as Zung, Beck, or even the relevant subscales for paranoia and depression from MMPI. In fact, our initial understanding [3] was to rely on the MMPI subscales, which appeared clinically valid and capturing states and traits at the same time. However, we have privileged the von Zerssen scale for two reasons. On one hand, it was relatively brief in terms of items number and more concise as item responses when compared to the Beck Depression Inventory, for instance. As we are aware, BDI is meant to monitor the effect of CBT whereas von Zerssen scale is meant to monitor primarily the effect of pharmacological therapy, and therefore, the items are far more condensed reflecting the core psychopathological phenomena. On the other hand, the scale had two counterparts, specifically designed to capture the two main syndromes in psychopathology: depressive (DS) and paranoid (DP). Therefore, we assumed that it is more likely to produce a contrast in the BOLD signal when administered simultaneously with fMRI acquisition (technically as block designed fMRI task). The hypothesis in this scenario states that while self-assessment evaluation is performed, the results could be cross-validated by certain neural activations in response to the subscale items. First, we applied this paradigm to try and differentiate depressed patients from healthy controls (HCs). The DS subscale was used versus neutral items from a general interest's scale (diagnostically neutral (DN)) while concurrently performing fMRI [9]. This method was then expanded by including the DP subscale (DP condition) and using it for the differentiation between DEP and SCZ [10]. Findings were intriguing with notable activations during DP stimuli in SCZ (right angular gyrus (AG), left posterior cingulate (PCC) and precuneus (PRC), and right transverse temporal gyrus) differing from those in depression items (left middle cingulate and right superior temporal gyrus).

Furthermore, a multivariate analysis was performed aiming to develop a bottom-up machine learning model through the extraction of brain signatures from three principal components, generated by analyzing the activations provoked by the three distinct groups of stimuli (DS, DP, and DN) [11]. This model's purpose was the subsequent production of cross-validation markers and a classification of mental disorders using the brain signatures corresponding to clinical evaluation tests.

Further along, independent component analysis (ICA) was implemented, as it is different from classical voxel–based activation analysis in a way that focuses on temporally coherent spatial networks that are activated in response to tasks performed during fMRI. The task-related results showed one component comprising of the right superior and middle temporal gyri, the left middle and inferior frontal gyri, and the right anterior insula, which was shared between all conditions. The component related to DS and DP conditions was composed by frontal/motor and parietal regions, and one component was only modulated by the DP condition and corresponded to prefrontal regions. Two components modulated by the DS condition included the PCC and PRC, occipital areas (lingual and fusiform) [12].

These results propose various possibilities for further implementation, discussed in our recent review [13]. Our hypothesis suggests that patient response to DS, DP, and DN could be cross-validated when performed concurrently with task-based fMRI, resulting in specific and common neural activations in response to the PDS items. In the current study, we tried to overcome one of the limitations of our previous one, namely the lack of a HC group. Thus, our aim was to investigate the possible differentiating results between patients (SCZ and DEP) and HCs using ICA.

1.1. Subjects and Methods

1.1.1. Subjects. A total of 72 subjects participated in this study, including 21 HCs, 26 patients with SCZ, and 25 patients with DEP. Each subject underwent a comprehensive evaluation by board-certified psychiatrists, utilizing the Mini-International Neuropsychiatric Interview [14] and the Montgomery–Åsberg Depression Rating Scale (MADRS) [15]. The exclusion criteria were defined as a previous history of comorbid mental disorders (considered for HCs and patients separately), systematic and organic neurological diseases, cranial trauma, or MRI-incompatible metal implants. All participants provided written informed consent in accordance with the Declaration of Helsinki. The study was approved by the Medical University of Plovdiv Ethical Committee (2/19.04.2018).

2. Methods

2.1. MR Scanning. Patients were scanned on a 3T MRI system (GE Discovery 750w), starting with a high-resolution

structural scan (Sag 3D T1 FSPGR sequence), slice thickness 1 mm, matrix 256 × 256, relaxation time (TR) 7.2 ms, echo time (TE) 2.3, and flip angle 12°, followed by a functional scan (2D EPI sequence), with slice thickness 3 mm, matrix 64 × 64, TR 2000 ms, TE 30 ms, and flip angle 90°.

2.2. fMRI Task. The paradigm consisted of three different active conditions and one rest condition, with a total duration of 11 min and 44 s presented in a classic block design. Each active block lasted for 32 s and contained four text statements of 8 s. The statements of the depression-specific (DS) and the paranoia-specific (DP) blocks were taken from the von Zerssen depression and paranoia subscales accordingly [7]. As in our previous study [9], there were also DN blocks consisting of four statements from a questionnaire about general interests and likes. Under each written statement, four possible answers ("completely true," "mostly true," "somewhat true," and "not true") and the respective four response buttons (upper left, lower left, lower right, and upper right) were presented. In total, there were four blocks of each type, and they were alternating between the three active conditions. After each active block a 20-s resting block (OFF) with a fixation cross in the middle of the screen (DS_OFF_DN_OFF_DP_OFF_DS...)

2.3. Image Processing. Data were analyzed using the SPM 12 software (Statistical Parametric Mapping, http://www.fil.ion.ucl.ac.uk/spm/) running on MATLAB R2021 for Windows. The preprocessing included the following steps: realignment of the functional data for correction of head motion, coregistration between the high-resolution anatomical image and the functional scans, intraindividual estimation of spatial registration parameters based on the anatomical image, and transformation of the coregistered functional data to standardized Montreal Neurological Institute (MNI) space, followed by spatial smoothing with a 8-mm full-width-at-half-maximum Gaussian kernel.

2.4. Data Analysis. In our study, we conducted an analysis of the variations in brain activation patterns observed during the experimental conditions among three distinct subject groups: HCs, SCZ patients, and DEP patients. Initially, we sought to identify the brain networks that were activated in response to the task across all subjects. Subsequently, we drew comparisons between the diagnostically specific (DS) blocks, the DN blocks, and the DP-specific blocks. Finally, we employed the GIFT toolbox and statistical parametric mapping to compare the activity levels of regions within the identified brain networks between the three groups (SCZ, DEP, and HC). Please refer to the sections below for further details.

2.5. ICA. Group ICA was conducted to identify brain networks activated in response to a task (DS-DP, DN-DP, DS-DN). ICA was performed on the BOLD fMRI scans of all 75 subjects using GIFT (http://trendscenter.org/software/gift). Individual ICA was computed using the Infomax algorithm [16]. For the group ICA, all subjects were analyzed concurrently, and principal component analysis (PCA) was used for compression. ICA aims to decompose a multiple signal into independent, mostly non-Gaussian signals. The number of components selected was 20. The component time courses were subjected to multiple regression analysis to assess the task-modulated components. Regression slopes were calculated for the conditions, and beta-weights were obtained for each component. These beta values were then analyzed using a one-way ANOVA (groups) across the groups to identify statistically significant effects at a false discovery rate (FDR)–corrected p value of less than 0.05. The areas corresponding to component activity were extracted in MNI and Talairach coordinates using the "Write Talairach Table" procedure in GIFT with the following parameters: threshold (3.5) and the distance between the contiguous voxels (4 mm).

2.6. Statistical Analysis

2.6.1. GIFT Analysis. The component time courses were analyzed using multiple regression to assess the components modulation by the task. We calculated regression slopes for the conditions and obtained beta-weights for each component. The resulting beta values were subjected to one-way ANOVA (groups) across the groups to determine significant effects at a FDR-corrected $p < 0.05$. Consequently, only the components significantly associated with task performance remained out of the initial 20 components.

2.6.2. SPM Analysis. We utilized the statistical parametric mapping SPM 12 software (Statistical Parametric Mapping, http://www.fil.ion.ucl.ac.uk/spm/) to analyze the ICA component maps, aiming to identify clusters of voxels (brain regions) exhibiting significant differences in response to the task among the HC, SCZ, and DEP subject groups, as revealed during the GIFT analysis. The analysis involved factorial design specifications, employing a two-sample t-test with two groups and a one-way ANOVA test (HC-DEP, HC-SCZ, and DEP-SCZ). The volumes of significantly altered components identified in the DS-DP, DN-DP, and DS-DN comparisons during the ICA analysis step served as input data. An implicit mask was set by default, and global normalization was not applied. Statistical significance was determined by a cluster-forming threshold of uncorrected p value less than 0.05 and a peak level of $p < 0.001$ uncorrected.

3. Results

3.1. Demographic and Clinical Characteristics. There have been no significant differences identified between the three groups in terms of their age, sex, and education level distribution (Table 1).

3.2. ICA Results. We have successfully extracted 20 independent components for each subject, representing distinct neural circuits exhibiting consistent activation patterns. To assess the task-modulated components, we employed multiple regression analysis on the component time courses. Subsequently, we sorted the components based on various regressors (DS, DP, and DN) and identified the following viable components: 6, 7, 9, 16, and 20. The corresponding time series and active brain regions for these components

Table 1: Demographic characteristics of the groups.

	Healthy controls ($n = 21$)	Schizophrenia ($n = 25$)	Major depressive episode ($n = 26$)	Significance
Age (mean ± SD)	33.81 ± 10.69	37.52 ± 12.25	40.88 ± 12.26	0.133[a]
Sex (M/F)	14/7	13/12	12/14	0.360[b]
Education (years)	16 ± 3.50	25 ± 3.28	25 ± 3.36	0.493[a]

Abbreviation: SD, standard deviation.
[a]One-way ANOVA test.
[b]χ^2 test.

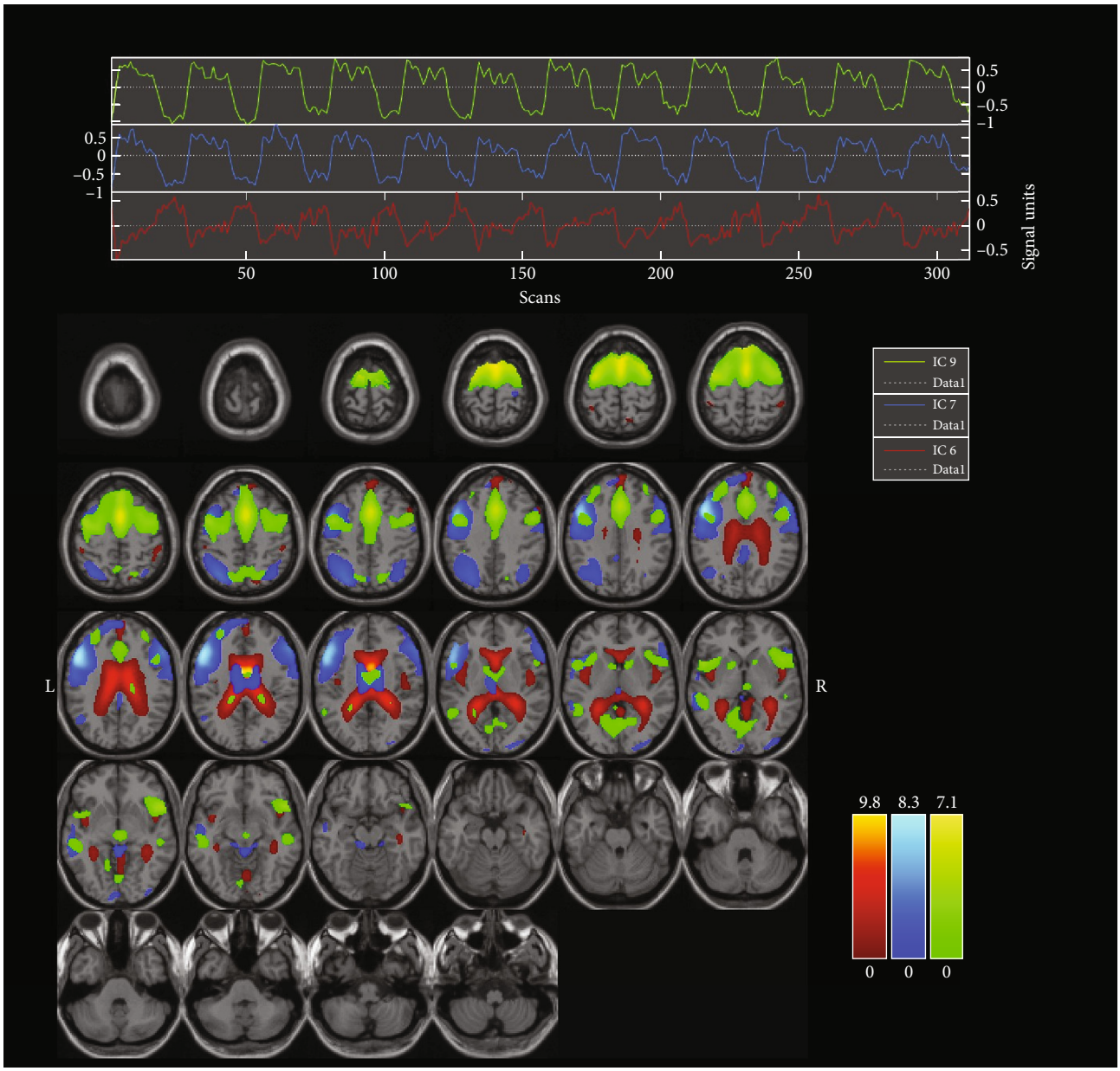

Figure 1: Map of the components, significantly modulated by the task-specific conditions (DS, DN, and DP).

are presented in Figures 1 and 2, as well as in the accompanying Tables 2 and 3.

The statistically significant findings from the one-way ANOVA (groups) test revealed notable differences between specific groups and components. In particular, the comparisons between SCZ and HC, as well as D and SCZ, yielded noteworthy results. For the SCZ-HC comparison, the following components exhibited significant differences: DS-DP

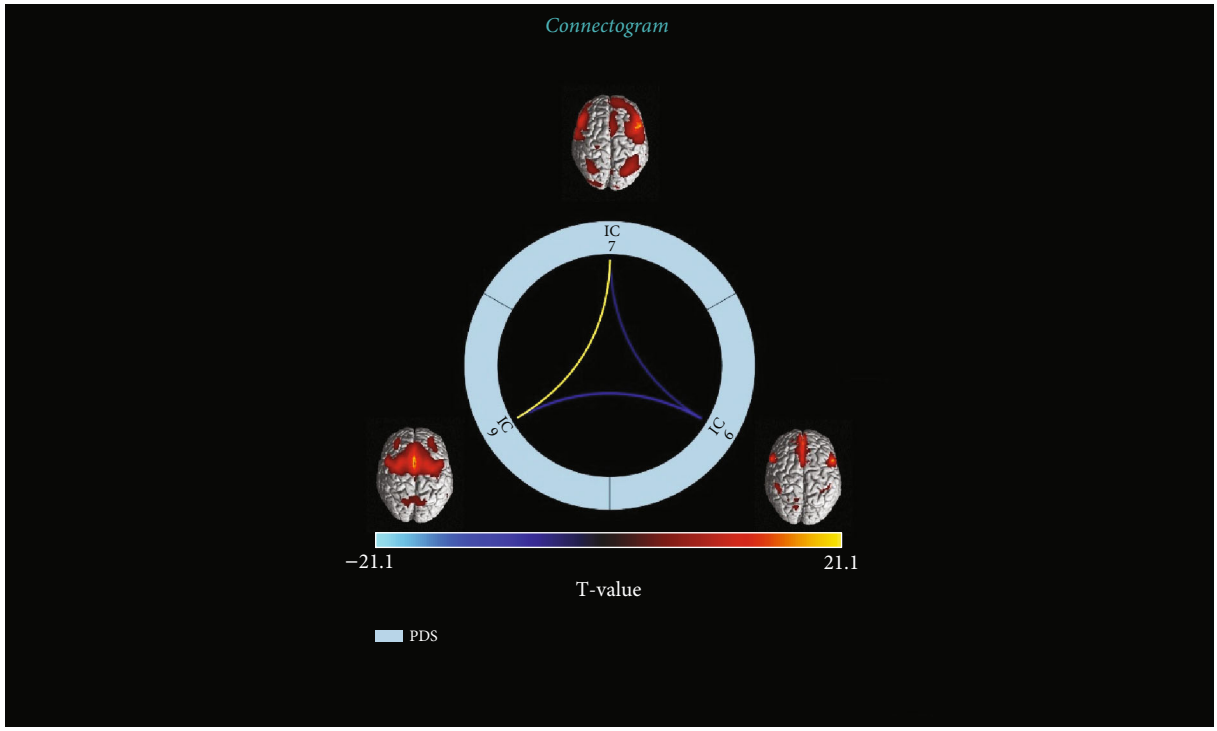

Figure 2: Connectogram of the significantly different components (T-scores were employed, with a threshold set at 3.5; yellow line: positive loading; blue line: negative loading).

Table 2: Components with significant difference between groups with corresponding reference in the text.

Component	p value*	Condition	Between group comparison
Component 6	0.024448	DS-DN	SCZ-HC
	0.010160	DP-DN	
	0.014018	DS-DP	
Component 7	0.030302	DS-DN	D-SCZ
Component 9	0.030125	DP-DN	D-SCZ
	0.039329	DS-DP	

*FDR-corrected p value of less than 0.05.

(components 6, 13, and 17), DS-DN (components 5, 6, and 17), and DP-DN (components 6, 13, and 17). In the comparison between D and SCZ, the following components showed significant differences: DS-DP (components 5, 9, and 20), DS-DN (components 7 and 19), and DP-DN (components 1, 2, 9, 11, and 12). In the comparison between D and HC, no task-related components survived. However, of all those significantly different components, only 6, 7, 9, and 20 were identified as viable during the previous step of analysis.

3.3. SPM Results. No significant clusters were found for the relevant components, as well as contrasts.

4. Discussion

The current study yielded several important outcomes. Five components were identified as task-related through ICA, but only three of them were found to demonstrate statistical difference between SCZ, DEP and HC, namely components 6, 7, and 9. The contrast between SCZ and HC was presented by Component 6, which exhibited significant difference when comparing all three active conditions. On the other hand, SCZ and DEP group differences were presented by Component 7 for DS-DN comparison and Component 9 which highlighted alterations in activation related to the DP-DN and the DS-DP comparison. However, in the comparison of DEP versus HC, no task-related components survived the one-way ANOVA test.

One of the most intriguing findings in our research is the information revealed by component 6. It indicates that the areas it corresponds to the cingulate gyrus, the basal ganglia including caudate and lentiform nuclei, have an impaired activation in the SCZ patient population, compared to HC, regardless of the specific task–related stimuli.

The cingulate gyrus consists of anterior cingulate cortex (ACC) and PCC cortex, represented in Component 6 by Brodmann areas (BAs) 24 and 23, respectively. ACC is involved mainly in cognitive behavior and emotional regulation [17]. Notably, ACC is a part of the salience network (SN) [18], while the PCC is a component of the default mode network (DMN) [19].

These two large-scale networks are found to have significant deficits in SCZ patients [20]. They have been linked to the clinical symptoms of this mental illness such as positive, negative, and cognitive ones [21]. In addition, evidence was attained of the disruption of the central executive network (CEN) and SN in the early stages of the illness [22] as well as in individuals at high risk of psychosis [23].

Table 3: Characteristics of the significant components (regions with the highest level of activity within each component).

	Brain area	Brodmann area	Volume (cc)	Random effects: Max value (x, y, z)	MNI (x, y, z)	Loading
Component 6	Lateral ventricle	*	7.4/6.7	23.2 (−2, 3, 16)/23.4 (4, 3, 16)	(−2, 2, 18)/(4, 2, 18)	+
	Extra nuclear	*	10.1/9.2	18.3 (−2, 10, 14)/14.7 (24, −36, 15)	(−2, 10, 16)/(24, −38, 14)	+
	Caudate	*	1.4/2.0	15.8 (−10, 1, 20)/16.0 (6, 6, 13)	(−10, 0, 22)/(6, 6, 14)	+
	Cingulate gyrus	23, 24	1.5/1.5	10.0 (−12, −10, 26)/10.0 (16, −14, 27)	(−12, −12, 28)/(16, −16, 28)	+
	Subgyral	*	2.8/3.3	7.7 (−26, −48, 15)/8.1 (32, −39, 6)	(−26, −50, 14)/(32, −40, 4)	+
	Extra nuclear	*	1.2/1.6	5.5 (−6, 0, 4)/5.2 (2, −23, 1)	(−6, 0, 4)/(2, −24, 0)	−
	Lentiform nucleus	*	1.0/0.8	4.3 (−16, 12, −1)/4.2 (22, 11, −4)	(−16, 12, 0)/(22, 12, −4)	−
Component 7	Inferior frontal gyrus	6, 9, 10, 13, 44, 45, 46	10.3/5.5	18.6 (−51, 17, 25)/8.7 (53, 26, 21)	(−52, 16, 28)/(54, 26, 24)	+
	Middle frontal gyrus	6, 8, 9, 10, 46	13.2/3.2	17.3 (−51, 15, 29)/8.6 (53, 23, 23)	(−52, 14, 32)/(54, 22, 26)	+
	Subgyral_R	*	3.9	13.7 (−46, 24, 21)	(−46, 24, 24)	+
	Precentral gyrus_R	6, 9, 44	10.0	11.5 (−53, 16, 7)	(−54, 16, 8)	+
	Superior parietal lobule_R	7, 40	2.5	7.5 (−32, −66, 47)	(−32, −70, 48)	+
	Precuneus_R	7, 19, 39	1.7	6.7 (−26, −69, 48)	(−26, −74, 48)	+
	Inferior parietal lobule_R	7, 39, 40	3.4	6.6 (−38, −60, 47)	(−38, −64, 48)	+
	Superior frontal gyrus_R	6, 8, 10	2.1	5.5 (−34, 53, 14)	(−34, 54, 18)	+
	Middle frontal gyrus_L	6, 8, 9	1.7	7.4 (32, 41, 38)	(32, 40, 44)	−
	Superior frontal gyrus_R	6, 8, 9, 10	4.3	7.0 (24, 48, 36)	24, 48, 42)	−
	Middle occipital gyrus_R	19, 37	1.0	5.0 (−50, −68, 3)	(−50, −70, 0)	−
	Middle temporal gyrus_R	37, 39	1.4	4.8 (−50, −64, 3)	(−50, −66, 0)	−
Component 9	Superior frontal gyrus	6, 8	8.9/8.8	13.9 (−4, 17, 62)/13.9 (4, 13, 62)	(−4, 14, 68)/(4, 10, 68)	+
	Medial frontal gyrus	6, 8, 9, 32	3.0/3.2	11.5 (0, 8, 46)/11.0 (4, 14, 45)	(0, 6, 50)/(4, 12, 50)	+
	Middle frontal gyrus	6, 8, 9	7.4/6.5	10.8 (−26, 5, 62)/10.0 (30, 7, 60)	(−26, 2, 68)/(30, 4, 66)	+
	Cingulate gyrus	24, 32	3.4/3.5	9.7 (0, 4, 46)/10.5 (4, 16, 42)	(0, 2, 50)/(4, 14, 46)	+
	Precentral gyrus_R	6	1.6	6.9 (−38, −5, 57)	(−38, −8, 62)	+
	Inferior parietal lobule	7, 39, 40	3.1/2.4	7.0 (−42, −64, 47)/6.5 (48, −60, 44)	(−42, −68, 48)/(48, −64, 44)	−
	Precuneus_R	19, 39	1.2	6.6 (−38, −70, 42)	(−38, −74, 42)	−
	Angular gyrus	39	1.7/1.0	6.3 (−46, −68, 37)/5.9 (51, −60, 36)	(−46, −72, 36)/(52, −64, 36)	−
	Inferior frontal gyrus_R	10, 45, 46	1.2	5.2 (−51, 34, 13)	(−52, 34, 16)	−
	Precentral gyrus_R	4, 6	1.5	4.4 (−61, −10, 32)	(−62, −12, 34)	−

In 2011, Menon provided a comprehensive framework for understanding the interactions between the DMN, the SN, and the CEN, within various psychopathological conditions, introducing the triple network model [24]. This model underscores the pivotal role of the SN in switching between the DMN and CEN, with disruptions leading to cognitive and affective impairments observed in SCZ. Subsequently, in 2014, Nekovarova et al. [25] implied this model in their work, positing that dysfunctional switching between the DMN and CEN, driven by aberrant activity in the SN, is a unifying mechanism underlying various SCZ symptoms.

Having in mind this substantial evidence of SN dysfunction in SCZ and the understanding of the SN's extensive connectivity with other large-scale networks, enabling appropriate responses to salient stimuli [26], we propose that the alteration of Component 6 signifies an aberrant response to salient stimuli in SCZ patient population. This suggests that these patients may experience difficulty in switching between internal thoughts and external tasks.

The caudate and lentiform nuclei are part of the basal ganglia. They receive signals from different brain areas and send projections back to the cortex. Therefore, the basal ganglia are responsible for important functions, which are commonly altered in SCZ, mostly revolving around cognitive functioning, motor control and emotional processing [27]. Aberrant functional connectivity of the caudate nucleus (CN) and between the CN and other brain structures (e.g., the frontal gyrus) was reported in SCZ [28] as well as characteristic hemispheric specialization, which makes the CN a potential diagnostic biomarker for SCZ [29]. In addition, structural studies exploring the volume of the CN in SCZ patients discovered that alterations depend on duration of untreated psychosis, level of premorbid risk of developing a psychosis, and other determinants [30, 31]. Thus, it is no surprise that in our study the activity in the CN during tasks in the SCZ population was modulated no matter the specific condition contrast.

The lentiform nucleus (LN), as part of the basal ganglia, has a major impact on various aspects of cognition. Furthermore, it exhibits a substantial population of dopaminergic neurons, and SCZ is generally associated with abnormalities in the transmission of dopamine. Accordingly, a recent study [32] explored the fractional amplitude of low-frequency fluctuation (fALFF) of bilateral LN, finding increased activity, which were positively correlated with test scores illustrating neurocognitive impairment through digit span–backward repetition.

Both DEP and SCZ have been associated with lower gray matter volume of the LN [33, 34] and hypoconnectivity in the LN and striatum in general [35, 36], indicating that the difference, exhibited in Component 6 in our study, could be a result of variation of the activation pattern to DS stimuli in the task.

Ultimately, in Component 6, there is unusual activation in both DMN and SN, which are large-scale networks with deeply intertwined functions, whereas the SN in particular is believed to act as a switch between the DMN and the CEN. All of these networks are by some means dysfunctional in SCZ, which is thoroughly described by various authors in the triple-network model. In our research, Component 6 exhibited unique activity in SCZ patients, compared to HC, in response to all three types of stimuli. It is important to keep studying the areas, contained in these networks; their connections to one another; their activity; and the influence of different stimuli on them as they could help explicitly separate SCZ from healthy individuals and other mental conditions and point to important aspects of the pathophysiology and physical aspects of this disorder.

The other important finding of our study was that Component 7 sets apart SCZ and DEP populations on the contrast DS-DN. This shows us that the two groups have different responses to the DS stimuli, compared to the neutral ones. The regions of this component include areas involved both in the CEN (superior, middle, and inferior frontal gyri) and in the DMN (PRC and middle temporal gyrus) redirecting our attention to the triple-network dysfunction model of SCZ [23].

Generally, in healthy adults, the DMN is proven to be anticorrelated to the CEN [37], whereas it is also suggested that it directly inhibits the CEN [38]. Furthermore, in a 2015 study on the developments of large-scale networks over time [39], the DMN and CEN were found to become increasingly anticorrelated across early adolescence.

There have been several studies that present reduced functional and anatomical connectivity within the DMN in SCZ [40]. This phenomenon could also be related to morphological changes in the brain structures in SCZ [41]. In DEP, on the other hand, hyperactivation of the DMN is a common finding [42]. Moreover, there is evidence of attenuated activation of the CEN in depressed patients [43, 44] and, on the contrary, increased CEN functional connectivity within SCZ population [45].

The evidence presented thus far showcases the contrasting patterns of CEN and DMN activation in SCZ and DEP patient populations, consistent with the results derived from Component 7. However, it is crucial to acknowledge that research of brain functional connectivity presents some conflicting findings, and our results are based on task-related fMRI rather than resting-state fMRI.

While Component 7 demonstrated significant difference between the two patient groups in the contrast between the DS and neutral condition of the task, Component 9 on the other side proved to be different in both DP conditions versus the DS and the neutral one. This component is comprised of various regions including motor, anterior cingulate, and dorsolateral cortex, along with angular and supramarginal gyri.

The occurrence of statistically significant differentiation between DEP and SCZ in both DP contrasts in Component 9 was interpreted as reflecting neural activations induced by DP questioning in one of the patient populations. This finding may be indicative of a neural correlation underlying the DP symptomatology in SCZ patients.

Generally, the dorsolateral prefrontal cortex (dlPFC) is associated with domain general executive functions, such as working memory, planning, and switching through different tasks. These are mental functions that tend to be impaired in psychiatric patients. There is evidence on hypoactivation of

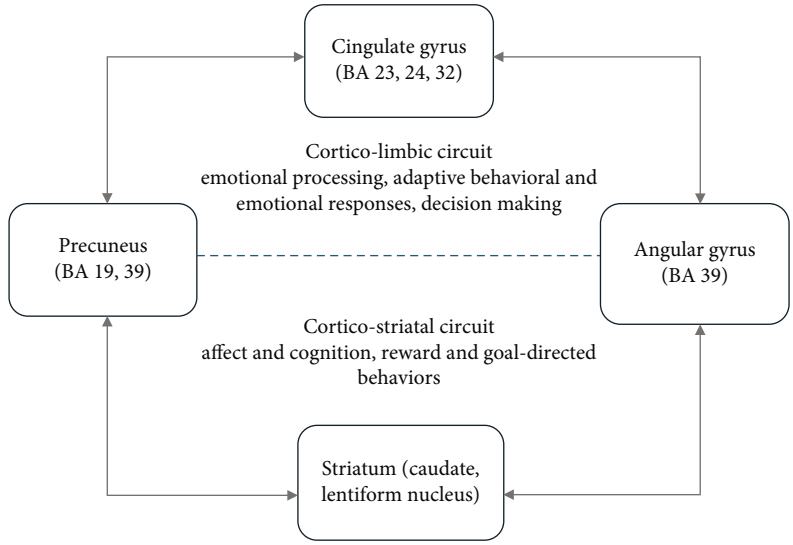

Figure 3: Brain circuits modulated by paranoid scale items.

the dlPFC in DEP with additional findings of increasing activation during recovery [46]. Moreover, SCZ patients also exhibit overall reduced activation of the dlPFC [47].

The AG, the supramarginal gyrus (SAG), and the prefrontal cortex are all elements of the heteromodal association cortex (HAC). HAC integrates data from different sensory modalities and is considered crucial for cognition [48]. Its pathophysiological involvement in SCZ has been hypothesized for many years, suggesting that such disruptions would lead to altered cognition, difficulties in forming a coherent perception, executive function deficits, impaired language, memory, and social interactions, all of which are congruent with symptoms seen in SCZ [49–53].

The SAG is located in the inferior parietal lobule, as is the AG, and corresponds to BA 40. As mentioned above, it is also a part of the HAC. It partakes in various cognitive and perceptual processes, including word processing [54], working memory [55], and empathy in the context of self-other distinction [56]. There is research that points to higher activation of the SAG in HC, compared to SCZ patients [57].

Generally, there has been proof that the inferior parietal cortex is involved in the sense of agency, thinking about others' emotions and viewing situations from a third-person perspective [58]. It is highly plausible that structural and functional abnormalities in the SAG and AG are linked to empathy and sense of self-care deficits observed in SCZ.

Overall, Component 9 displays the difference between the two patient populations in response to the DP stimuli. Expectedly, it is generally associated with brain areas responsible for executive functioning and various cognitive tasks, such as working memory and integration of sensory modalities, with a possible involvement of empathy execution dysfunction. These brain regions must be further investigated as possible targets for the treatment of paranoia in SCZ patients.

An intriguing outcome of our research is the lack of significant difference between the identified ICA components of HC and DEP groups, no matter the nature of the received stimuli. Previously, numerous studies have reported alterations in the brain activity of depressed patients in comparison to HC [59]. The reason behind this discrepancy could be rooted in the method used for the current research. For example, in a previous study of our group, in which there was variation in the fMRI results between the depressed and healthy groups, we used a two-sample *t*-test [60]. The two-sample *t*-test is more specific in the sense that it focuses on one comparison only and avoids the dilution of statistical power that might occur in ANOVA. Additionally, it's important to consider the phenomenological relationship between depression, HC, and SCZ. In our previous studies [12, 13], we have contrasted directly the BOLD activations or group independent components modulated by item responses which are also in two groups: SCZ and depression. That direct comparison produced series of meaningful results. However, during the peer review of our last publication on the topic [12], we have received recommendation to add control population, especially for SCZ. The addition of HCs and the respective three groups complicated the analysis, with the use of ANOVA tools. As we are aware, those are less likely to be specific in terms of discrimination power. In that regard, this is not a negative finding but rather a case of phenomenological continuum, since the spectrum of depression is far more "common sense" condition than paranoid syndrome, and therefore is less likely to produce contrasts on the level of ANOVA with the three groups under consideration: SCZ, depression, and HCs.

In summary, the networks related to the two clinical syndromes may be identified as follows (Figures 3 and 4):

1. Circuits 1 and 2: cortico-striatal and cortico-limbic circuit (Figure 3). It is processing preferentially items relevant to the core presentation of paranoid syndrome and includes basal ganglia (LN, caudate), cingulate cortex, PRC, and AG. It is modulated by the item responses to DP scale when compared to DS scale and DN items. The subcortical CN and cingulate

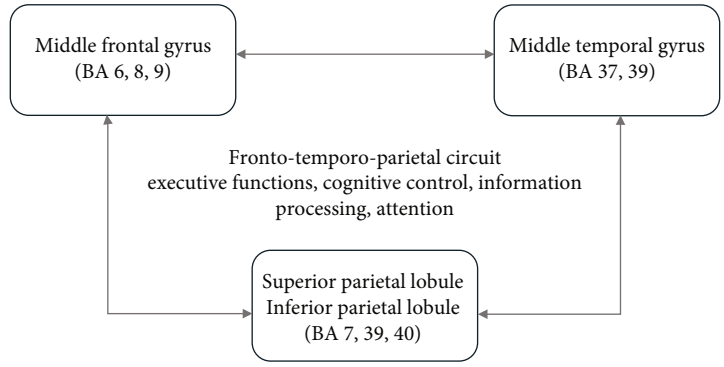

Figure 4: Brain circuits modulated by the depression scale condition.

cortex appear to have positive load (activated), whereas AG and PRC seem to be inhibited (negative load). That is consistent with our earlier findings [61]. With a simpler design, on direct comparison of two patient groups, with SPM, there has been reported contrast of the activations of PRC and AG between SCZ and depression. It is relevant to the fundamental self-referential disturbance underlying paranoid delusions and prevalent limbic/subcortical disinhibition, which is in line with the dominant theories about pathogenesis of SCZ.

2. Circuit 3 (Figure 4): fronto-temporo-parietal circuit, preferentially involved in the processing of the DS scale items. It consists of middle frontal gyrus (positive load, activation), prominent among other frontal areas of the brain; middle temporal gyrus; and various parietal regions (mainly negatively loaded). This is also consistent with our previous findings with structural and functional MRI, which outlined the activation of MFG in response to DS items in a case control study of patients with depression and HCs and also with our voxel-based morphometric study [62], which reported reduction in the gray matter volume in depressed patients affecting similar regions. It may be regarded relevant to the cognitive distortions that underlie dysfunctional thoughts in depression.

5. Conclusion

This study utilized the PD-S in order to understand two severely disabling mental conditions (depression and SCZ) on a deeper level. The comparison was not limited to patient populations only but included HC to have an observation of the effect of the DS, DP, and DN stimuli on healthy individuals too. Our results demonstrate differences in brain circuits processing preferentially diagnostic stimuli across the three groups. Those circuits involve mainly networks of cognitive functioning. Unsurprisingly, globally identified large-scale networks (the DMN, SN and CEN) are presented in these components, which provides insights in their role for pathophysiology of SCZ and D. This evidence fosters the theory of transdisciplinary validation, where neurobiological measure such as functional MRI is determined as external validity operation for the diagnostic assessment scales. This can facilitate the use of clinical evaluation methods as proxy measures of brain functions.

The transdisciplinary validation can ultimately inform possible revisions of psychiatric inventories and classifications. A number of independent replications with larger scale of similarly designed studies is essential for the development of this area in neuroscience and psychiatry. As a result, the clinical self-assessment scales with established fMRI correlates will be validated as possible proximal measures of brain dysfunction.

5.1. Limitations. The small sample size should be mentioned as one of the limitations in this study. Also, the depression severity was assessed with MADRS only in the population with DEP and the HCs. It is clear that some patients with SCZ may have experienced depressive symptoms as well. Also, as a general limitation in the field, the lack of consensus in normative basis for fMRI or psychopathological studies should be exposed [63].

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon a reasonable request.

Conflicts of Interest

The authors declare no conflicts of interest.

Author Contributions

D.S. conceived the study; led the study team; wrote significant parts from the introduction and discussion; critically revised the manuscript; and supervised the study; R.P. performed the data analysis and contributed to the first version of the manuscript. S.K. contributed to the design and the quality control of the study and critically revised manuscript. G.Z. and D.N. codrafted the introduction and discussion. S.A.K. and V.K. contributed to the statistical analysis and data interpretation and critically revised the manuscript. All authors read and approved the final version of the manuscript.

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