Title:

Effective Connectivity Between the Orbitofrontal Cortex and the Precuneus Differentiates Major Psychiatric Disorders: Results from a Transdiagnostic Spectral DCM Study

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Abstract

• Background & Objective

We have previously identified aberrant connectivity of the left precuneus, ventrolateral prefrontal cortex, anterior cingulate cortex, and anterior insula in patients with either a paranoid (schizophrenia), or a depressive syndrome (both unipolar and bipolar). In the current study, we attempted to replicate and expand these findings by including a healthy control sample and separating the patients in a depressive episode into two groups: unipolar and bipolar depression. We hypothesized that the connections between those major nodes of the resting state networks would demonstrate different patterns in the three patient groups compared to the healthy subjects.

• Method

Resting-state functional MRI was performed on a sample of 101 participants, of which 26 patients with schizophrenia (current psychotic episodes), 24 subjects with bipolar disorder (BD), 33 with major depressive disorder (MDD) (both BD and MDD patients were in a current

depressive episode), and 21 healthy controls. Spectral Dynamic Causal Modeling was used to calculate the coupling values between eight regions of interest, including the anterior precuneus (PRC), anterior hippocampus, anterior insula, angular gyrus, lateral orbitofrontal cortex (OFC), middle frontal gyrus, planum temporale, and anterior thalamus.

• Results & Conclusion

We identified disturbed effective connectivity from the left lateral orbitofrontal cortex to the left anterior precuneus that differed significantly between unipolar depression, where the influence was inhibitory, and bipolar depression, where the effect was excitatory. A logistic regression analysis correctly classified 75% of patients with unipolar and bipolar depression based solely on the coupling values of this connection. In addition, patients with schizophrenia demonstrated negative effective connectivity from the anterior PRC to the lateral OFC, which distinguished them from healthy controls and patients with major depression. Future studies with unmedicated patients will be needed to establish the replicability of our findings.

Keywords: Effective connectivity, transdiagnostic, schizophrenia, bipolar disorder, major depression, resting state MRI, spectral Dynamic Causal Modeling, precuneus, orbitofrontal cortex

Main Text

1. Introduction

Psychiatric conditions have long been a major public health concern across the globe. Mental illness affects almost 450 million people worldwide and accounts for 14% of the global disease burden and 30% of the burden of non-fatal diseases [1]. Nearly one-third of patients with serious mental illnesses end up with long-term impairment and/or drug dependence [2]. Depression and schizophrenia (SCZ) have a severe impact on patients' quality of life, as well as far-reaching consequences for the individuals affected by the condition, their families, social care, and the broader community [3,4]. Several trials have shown that existing pharmacological interventions have substantial weaknesses in terms of recovery and remission [5]. Approximately 74% of those suffering from chronic SCZ experience problems with

compliance [6]. Furthermore, as little as 31 % of patients with major depressive disorder (MDD) recover after a 14-week treatment with a selective serotonin reuptake inhibitor [7].

Both the diagnostic and therapeutic methods and tools in psychiatry remain outside the conventional medical framework due to their low biological validity. Thus, psychiatric practice is designated an isolated position from other medical disciplines. Mental disorders, unlike other diseases, are divided into diagnostic categories defined by phenomenological criteria. However, the clinical presentation of mental disorders is not only heterogeneous but is also associated with a high prevalence of symptomatologic overlap.

To complicate things further, psychiatric disorders often have a high comorbidity rate. For example, around 50% of schizophrenic patients exhibit depressive symptoms, and approximately 50 % are diagnosed with a comorbid substance use disorder at some point in their lives [8,9]. The concurrent manifestation of two or more mental illnesses is linked to increased severity, poor pharmacological treatment response, and significant suicide risk as opposed to the presence of a single condition [5]. This, along with the incomplete understanding of the neurochemical aberrations that underpin psychiatric disorders, contributes to the existing pharmacotherapeutic inefficacy. Therefore, the necessity for an evidence-based theoretical foundation has led to a paradigm shift utilizing transdisciplinary translation to close the existing explanatory gap [10]. The discovery of biomarkers in psychiatry has become extremely relevant for the diagnostic and therapeutic outcome of patients [5].

In recent decades, a multitude of studies aiming to establish objective biomarkers in the field of psychiatry with the use of different neuroimaging techniques have yielded inconsistent results. However, functional magnetic resonance imaging (fMRI) has made significant contributions to our understanding of the putative neuronal mechanisms causing depressive symptoms, avolition, and cognitive impairments in people suffering from mood disorders. More specifically, changes in interregional connectivity may be a promising method for capturing the impact of MDD and bipolar disorder (BD) at a systems-level [11]. The science of large-scale neural networks provides a robust model for characterizing the neurobiology of psychiatric conditions [12] in order to map the diverse manifestations of mood and psychotic disorders, given that their symptoms are the result of aberrations in cognitive processes. [13]. This model emphasizes the importance of three networks that perform different roles in human cognition by mapping salient external and internal events - the Salience Network (SN),

executing cognitive control - the Central Executive Network (CEN) and the Default Mode Network (DMN), the activity of which increases during rest and decreases during task performance [14].

There are two main approaches to studying neural networks – functional connectivity (FC), which reflects the temporal correlations of neuronal activity, and effective connectivity (EC), which refers to the influence one neural system exerts over another i.e. the direct causal influence [15]. Along with Granger causality and other methods, the dynamic causal modeling (DCM) approach has been largely used for the assessment of effective connectivity in task-related but also, to an increasing extent, in resting-state fMRI [16,17]. DCM was developed for estimating coupling among brain regions and how that coupling is influenced by experimental changes (in task-related fMRI). The main idea is to construct fairly realistic models of interacting nodes (regions). The models defined in this manner are then supplemented with a forward model reflecting the match between the hidden states of each node (e.g., neuronal activity as reflected by the canonical hemodynamic response function) and the measured responses. This enables the best model and its parameters (i.e., effective connectivity) to be identified from observed data [17]. With respect to resting-state fMRI, spectral DCM has been found to be more accurate and more sensitive to group differences compared to stochastic DCM [18].

A recent functional connectivity study has been able to identify increased FC in the CEN, mainly left ventrolateral and dorsolateral prefrontal cortex (VLPFC and DLPFC), in bipolar patients and increased FC in the DMN (in the precuneus) along with reduced connectivity of the cingulo-opercular network to default mode regions (anterior cingulate cortex, posterior cingulate cortex, and inferior parietal cortex bilaterally) in unipolar patients [19]. In a seed-based study of the hippocampus (HPC) Fateh et al. reported that MDD was associated with an increased FC between right anterior HPC and lingual gyrus compared to BD and healthy controls (HC) [20]. Interestingly, local FC was increased across SCZ, BD, and MDD within the bilateral orbital frontal cortex (OFC) and decreased in the primary visual, auditory, and motor cortices, right supplemental motor area, and bilateral thalami compared to healthy controls. Moreover, the gradient of the changes was most pronounced in SCZ and less so in BD and MDD [21].

In our previous research using spectral DCM (In press), we have been able to identify aberrant connectivity from the left precuneus to the left middle frontal gyrus (VLPFC) and from the left anterior insula (AI) to the left precuneus (PRC), both inhibitory connections, in

patients with the depressive syndrome in the context of MDD and BD, as well as excitatory connection from the anterior cingulate cortex (ACC) to the AI in patients with paranoid SCZ. To replicate and expand these findings, we performed the current study, including HC and separate groups of patients with BD and MDD. We hypothesized that the connections between the major nodes of the DMN, SN, and CEN will demonstrate different patterns in the three patient groups compared to the healthy subjects.

2. Participants and methods

2.1 *Participants*

A total of 101 participants including twenty-four subjects with SCZ (mean age 38.8 ± 14.0, 12 males), twenty-three with BD (mean age 42.8 ± 11.9, 8 males), thirty-three with MDD (mean age 46.6 ± 13.4, 12 males) and twenty-one HC (mean age 39.0 ± 13.1 y, 5 males) were recruited for the present study. Participants were assessed by two experienced psychiatrists (D.S., S.K.) using a general clinical interview and the structured Mini-International Neuropsychiatric Interview (M.I.N.I 6.0) [22]as well as the Montgomery–Åsberg Depression Rating Scale (MADRS) [23] and the Positive and Negative Syndrome Scale (PANSS) [24]. The diagnosis was based on the clinical interview, the presented medical documentation and additional information from accompanying family members (if available) and complied with DSM-IV TR criteria.

Patients with SCZ presented with a current psychotic episode, while patients with BD and MDD were enrolled during a depressive episode as assessed by the Bulgarian Translation of the short version of M.I.N.I 6.0. The interview was also used to rule out psychiatric comorbidities such as panic disorder, agoraphobia, social phobia, generalized anxiety disorder, obsessive compulsive disorder, posttraumatic stress disorder, eating disorders (anorexia and bulimia), alcohol or other substance use disorders as well as the dissocial personality disorder.

Depressive symptom severity was assessed with the MADRS - a 10-item clinician rated scale broadly used both in practice and research settings. The cut-off value for the total MADRS score was set to 20 (above which depression is considered moderate or severe). Psychotic symptoms were assessed using the PANSS, which allows for detailed scoring of different positive, negative, and general symptoms. To ensure a reasonable severity of the

psychotic episode, a minimum rating of 3 was required for P1 (delusion) and/or P6 (suspiciousness). Patients were on a stable antidepressant and/or antipsychotic regimen for at least 14 days before inclusion.

Subjects were excluded in the following cases - age under 18 or above 65 years, presence of metal implants or body grafts (e.g., pacemaker) incompatible with MRI, history of a psychiatric disorder (only for healthy controls), comorbid mental disorder as identified by the clinical interview and the M.I.N.I., severe somatic or neurological disease, and traumatic brain injury with loss of consciousness. Prior to inclusion, each of the participants provided written informed consent complying with the Declaration of Helsinki. The protocol of the study was approved by the University's Ethics Committee.

2.2 ***MRI data acquisition***

Subjects were scanned on a 3T MRI system (GE Discovery 750w) and the protocol included the following sequences: 1) high-resolution structural scan (Sag 3D T1 FSPGR, slice thickness 1 mm, matrix 256x256, relaxation time (TR) – 7.2 msec, echo time (TE) - 2.3 msec, flip angle 12^{o}, and 2) resting state functional scan - 2D Echo Planar Imaging (EPI), with slice thickness 3 mm, matrix 64x64, TR - 2000 msec, TE – 30 msec, 36 slices, flip angle 90^{o}, a total of 192 volumes. Before the EPI sequence, subjects were instructed to remain as still as possible with eyes closed and not to think of anything in particular.

2.3 Resting state data analysis

Data analysis was performed using the SPM 12 (Statistical Parametric Mapping, http://www.fil.ion.ucl.ac.uk/spm/) software running on MATLAB R2020 for Windows. During the preprocessing of the EPI images, they were realigned, co-registered with the structural scans, normalized to Montreal Neurological Institute (MNI) space, and smoothed with a 6 mm full-width-at-half-maximum Gaussian kernel.

During the postprocessing, a general linear model (GLM) was applied to the time series of each individual dataset. The covariates of no interest included the six rigid body motion parameters, average white matter, and cerebrospinal fluid signal time series. In the next step, the BOLD time series were extracted for eight predefined regions of interest defined as 6 mm radius spheres. These were the following left hemispheric regions with the corresponding MNI coordinates: anterior precuneus (PRC) (-10, -64, 24), anterior hippocampus (HPC) (-24, -11, -

18), anterior insula (AI) (-34, 22, 4), angular gyrus (ANG) (-26, -80, 42), lateral orbitofrontal cortex (OFC) (-40, 27 -8), middle frontal gyrus (MFG) – (VLPFC) (-41, 19, 41), planum temporale (PLT) (-54, -33, 15), thalamus - anterior nuclei (THL) (-6, -10, 2).

2.4 Dynamic Causal Modeling

Dynamic causal modelling (DCM) was performed as spectral DCM (spDCM) on the eight regions of interest listed above. The spDCM model was a fully connected model where each node was connected to every other node. Opposite to a stochastic DCM, a spDCM estimates effective connectivity from the cross spectra of the fluctuations in neuronal states rather than from their time courses directly [18]. Furthermore, the individual spDCM models were not separately but jointly estimated, using the Parametric Empirical Bayes (PEB) framework, implemented in SPM12. Finally, connectivity strengths (A-matrix) were extracted from the estimated spDCM models and further tested for statistical differences.

2.5 Statistical analysis

Statistical analysis of the demographic and clinical characteristics of the participants as well as of the connectivity strengths of the spDCM model was performed using IBM SPSS 22.0 for Windows. We used one-way ANOVA for continuous data, Chi-square test for categorical data, and Kruskal-Wallis test for nominal data in the four-group comparisons. Post-hoc tests (with Bonferroni correction) were performed where applicable to find differences between individual groups. We used binary logistic regression analyses with backward elimination based on the probability of the Wald statistic to predict the diagnostic group membership in the six possible two-group comparisons with independent variables and the connections identified by ANOVA. The level of significance was set to $p < 0.05$ for all tests.

3. Results

3.1 Demographic and clinical characteristics of participants

There were no statistically significant differences in age, sex, and education level in the four-group comparisons (Table1). We found statistically significant differences in the mean MADRS score in the three-group comparison of subjects with BD, MDD, and healthy controls. Post-hoc analysis with Bonferroni adjustment for multiple comparisons found this was due to

differences in the mean MADRS score between both patient groups on the one hand and HC on the other. No significant differences in mean MADRS scores between patient groups were found.

There were significant differences in the mean age of onset of disease in the three-group comparison of age of onset of disease between patients with SCZ, BD, and MDD (p=0.005). Post-hoc analysis with Bonferroni adjustment established that these were due to differences in the age of onset between SCZ and MDD patients (p=0.004). No significant differences were found between SCZ and BD patients (p=0.152) or between BP and MDD patients (p=0.711). We found no significant differences in the mean duration of illness between patients with SCZ, BD, and MDD. The mean duration of the current depressive episode did not differ significantly between patients with BD and MDD.

[Table 1]

Table 1. Demographic and clinical characteristics of the sample

	SCZ (n=24)	**BD (n=23)**	**MDD (n=33)**	**HC (n=21)**	**p**
Age (mean, SD)	38.8 ± 14.0	42.8 ± 11.9	46.6 ± 13.4	39.0 ± 13.1	0.092[a]
Sex (M/F)	12/12	8/15	12/19	5/16	0.338[b]
Education (years, SD)	12.8 ± 2.4	13.5 ± 2.3	14.0 ± 2.3	14.3 ± 2.0	0.141[a]
MADRS score (mean, SD)		30.3 ± 6.1	29.3 ± 7.0	0.5 ± 1.3	*0.000[a]
Age of onset (years)	24.9 ± 8.1	31.3 ± 10.9	34.9 ± 12.5		*0.005[a]
Duration of illness (months)	156.6 ± 116.1	131.1 ± 89.3	135.9 ± 100.2		0.484[a]
Duration of current episode (weeks)		15.7 ± 18.1	15.8± 17.0		0.974[d]

SD – Standard Deviation, [a] One-way ANOVA, [b] χ^2 - test, [c] Kruskal-Wallis test, [d] Independent-samples T test, MADRS - Montgomery–Åsberg Depression Rating Scale, * p<0.05.

3.2 Effective connectivity in healthy controls

The connectivity coupling values in the HC were tested against zero in a one-sample t-test which identified mainly self-inhibitory connections of seven of the eight nodes (except for

the thalamus), and several other inhibitory connections mainly involving the hippocampus, planum temporale and thalamus (see Table 2 for details). The only significantly different from zero excitatory connection was from the orbitofrontal cortex to the planum temporale. These results are illustrated in Figure 1A.

Table 2. Connections that were significantly different from zero in the healthy control group.

Connections	Mean	SD	[a] Significance
PRC ⊃	-0.197	0.342	0.016
HPC ⊃	-0.244	0.208	0.000**
AI ⊃	-0.243	0.345	0.004
ANG ⊃	-0.208	0.333	0.010
OFC ⊃	-0.179	0.272	0.007
MFG ⊃	-0.183	0.236	0.002
PLT ⊃	-0.187	0.251	0.003
HPC →PRC	-0.182	0.341	0.024
HPC →ANG	-0.192	0.291	0.007
HPC →OFC	-0.292	0.432	0.006
HPC →MFG	-0.274	0.364	0.003
AI → PRC	-0.175	0.340	0.029
OFC → PLT	0.196	0.320	0.011
MFG →PLT	-0.138	0.182	0.002
THL → ANG	-0.163	0.333	0.036
THL → OFC	-0.195	0.343	0.017

SD – Standard Deviation, [a] One sample t-test $p<0.05$, ** $p < 0.001$, ⊃ - self-inhibitory connection. PRC - precuneus, HPC - hippocampus, AI - anterior insula, ANG - angular gyrus, OFC - orbitofrontal cortex, MFG - middle frontal gyrus, PLT - planum temporale, THL – thalamus.

3.3 Effective connectivity in patients with major depressive disorder

The coupling connectivity strengths that significantly differed from zero in the group of patients with MDD are presented in Table 3 and Figure 1B. There were 21 significant connections, including self-inhibitory connections of all nodes, and both inhibitory and excitatory connections mainly engaging regions such as the precuneus, hippocampus, middle frontal gyrus, and orbitofrontal cortex.

Table 3. Connections, which were significantly different from zero in the MDD group.

Connections	Mean	SD	[a] Significance

PRC ⊃	-0.262	0.286	0.000**
HPC ⊃	-0.244	0.235	0.000**
AI ⊃	-0.224	0.305	0.000**
ANG ⊃	-0.204	0.243	0.000**
OFC ⊃	-0.244	0.285	0.000**
MFG ⊃	-0.256	0.273	0.000**
PLT ⊃	-0.212	0.273	0.000**
THL ⊃	-0.198	0.292	0.000**
PRC →ANG	0.201	0.345	0.002
HPC →PRC	-0.129	0.279	0.012
MFG →ANG	0.120	0.288	0.022
AI →OFC	0.152	0.272	0.003
MFG →OFC	0.074	0.204	0.045
HPC →OFC	-0.118	0.281	0.022
HPC →MFG	-0.205	0.368	0.003
AI → PRC	-0.154	0.225	0.000**
OFC → PRC	-0.121	0.193	0.001
MFG → PRC	0.086	0.242	0.050
AI →MFG	-0.178	0.328	0.004
THL → ANG	-0.188	0.418	0.014
THL → MFG	-0.158	0.430	0.043

SD – Standard Deviation, [a] One sample t-test $p<0.05$, ** $p < 0.001$, ⊃ - self-inhibitory connection. PRC - precuneus, HPC - hippocampus, AI - anterior insula, ANG - angular gyrus, OFC - orbitofrontal cortex, MFG - middle frontal gyrus, PLT - planum temporale, THL – thalamus.

3.4 Effective connectivity in bipolar patients

The group of BD patients exhibited a significant coupling strength in 13 connections, of which 7 were self-inhibitory (all nodes except the thalamus). The remaining 6 connections involved mainly the precuneus and the anterior insula. Detailed results are presented in Table 4 and Figure 1C.

Table 4. Connections that were significantly different from zero in the bipolar group.

Connections	Mean	SD	[a] Significance
PRC ⊃	-.235	0.296	0.001

HPC ⊃	-0.241	0.218	0.000**
AI ⊃	-0.246	0.202	0.000**
ANG ⊃	-0.247	0.308	0.001
OFC ⊃	-0.199	0.186	0.000**
MFG ⊃	-0.319	0.290	0.000**
PLT ⊃	-0.306	0.294	0.000**
OFC → PRC	0.113	0.243	0.036
PLT → PRC	-0.096	0.213	0.041
PRC → ANG	0.213	0.273	0.001
AI → OFC	0.253	0.281	0.000**
HPC →MFG	-0.189	0.329	0.012
AI → PLT	0.133	0.299	0.044

SD – Standard Deviation, [a] One sample t-test $p<0.05$, ** $p < 0.001$, ⊃ - self-inhibitory connection. PRC - precuneus, HPC - hippocampus, AI - anterior insula, ANG - angular gyrus, OFC - orbitofrontal cortex, MFG - middle frontal gyrus, PLT - planum temporale, THL – thalamus.

3.5 Effective connectivity in schizophrenic patients

The results from the one-sample t-test in the SCZ group yielded 17 connections that were significantly different from zero. These included 6 self-inhibitory connections (all regions except for the anterior insula and thalamus), excitatory connections engaging the middle frontal gyrus and the anterior insula, and mainly inhibitory connections involving the hippocampus and thalamus. A detailed description of the results is given in Table 5 and Figure 1D.

Table 5. Connections that were significantly different from zero in the schizophrenia group.

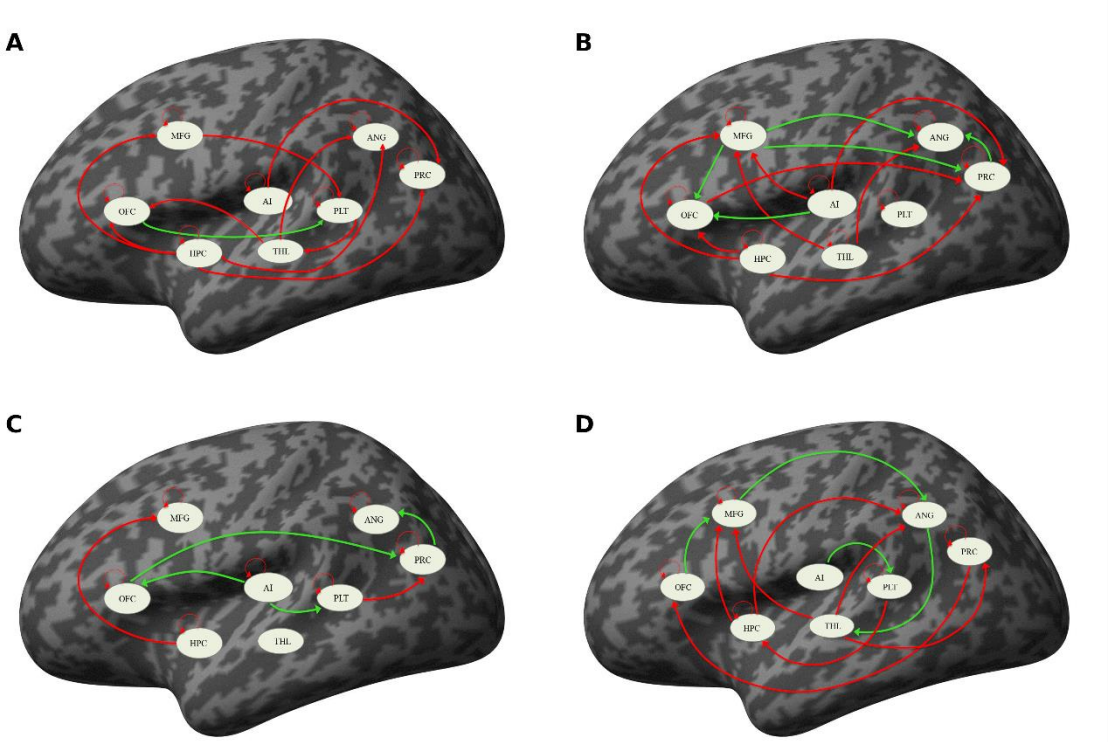
Connections	Mean	SD	[a] Significance
PRC ⊃	-0.282	0.269	0.000**
HPC ⊃	-0.124	0.285	0.043
ANG ⊃	-0.173	0.357	0.027
OFC ⊃	-0.179	0.284	0.005
MFG ⊃	-0.243	0.342	0.002
PLT ⊃	-0.212	0.287	0.001
PRC → OFC	-0.264	0.415	0.005
HPC →ANG	-0.224	0.263	0.000**
HPC →MFG	-0.245	0.347	0.002

AI → PLT	0.150	0.302	0.023
ANG → THL	0.071	0.147	0.027
OFC → MFG	0.201	0.353	0.011
MFG →ANG	0.232	0.342	0.003
PLT → HPC	-0.112	0.242	0.034
THL → PRC	-0.144	0.328	0.042
THL → ANG	-0.215	0.398	0.015
THL → MFG	-0.270	0.420	0.004

SD – Standard Deviation, [a] One sample t-test $p<0.05$, ** $p < 0.001$, ⊃ - self-inhibitory connection. PRC - precuneus, HPC - hippocampus, AI - anterior insula, ANG - angular gyrus, OFC - orbitofrontal cortex, MFG - middle frontal gyrus, PLT - planum temporale, THL – thalamus.

[Figure 1]

Figure 1. Connections significantly different from zero within the groups



A - healthy control, B - major depressive disorder, C – bipolar disorder, D – schizophrenia, red arrow – inhibitory influence, green arrow – excitatory influence

3.6 Differences in effective connectivity amongst the groups

One way ANOVA analysis of the mean coupling values identified significant differences in the following four connections: 1) from OFC to PRC (p= 0.001) 2) from THL to PRC (p=0.048) 3) from PRC to OFC (p=0.004) and 4) from HPC to PLT (p=0.013). The post hoc

analysis with Bonferroni correction for multiple comparisons found that the difference in the mean connectivity values of the first connection (OFC→PRC) was due to the contrast between the MDD group and both the SCZ (p=0.009) and the BD group (p=0.002). Notably, only the coupling strengths of the two groups of depressed patients were significantly different from zero with a positive mean (= excitatory connection) for the MDD and a negative mean (= inhibitory connection) for the BD group (given in bold in Table 6).

For the THL→PRC connection, the post hoc analysis demonstrated a trend towards significance p=0.057 between SCZ and BD groups. The difference in the PRC→OFC connectivity was driven by the contrast between the SCZ patients and both HC (p=0.006) and MDD patients (p=0.012). This connection was significantly different from zero only in the SCZ group having a negative mean value (= inhibitory connection). For the HPC→ PLT connection, the post hoc analysis identified significant differences between the healthy subjects and both SCZ (p=0.035) and BD patients (p=0.02) but there were no mean values significantly different from zero in any of the four groups (a trend towards significance p=0.06 in HC group).

Table 6. Connections demonstrating significant differences between the groups.

	HC (mean ± SD)	**MDD** (mean ± SD)	**BD** (mean ± SD)	**SCZ** (mean ± SD)	[a] **Significance**
OFC → PRC	-0.041 ± 0.172	**-0.122 ± 0.193**	**0.113 ± 0.243**	0.079 ± 0.300	SCZ vs MDD 0.009
					BD vs MDD 0.002
THL → PRC	-0.054 ± 0.334	0.037 ± 0.322	0.102 ± 0.290	**-0.144 ± 0.328**	SCZ vs BD 0.057
PRC→OFC	0.040 ± 0.257	-0.008 ± 0.284	-0.065 ± 0.211	**-0.264 ± 0.415**	SCZ vs MDD 0.012
					SCZ vs HC 0.006
HPC→ PLT	-0.189 ± 0.433	0.034 ± 0.305	0.108 ± 0.303	0.086 ± 0.265	SCZ vs HC 0.035
					BD vs HC 0.020

HC – healthy controls, MDD – major depressive disorder, BD – bipolar disorder, SCZ – schizophrenia, SD – Standard Deviation, [a] ANOVA post hoc with Bonferroni correction $p<0.05$, Bold – connections significantly different from zero, PRC - precuneus, HPC - hippocampus, OFC - orbitofrontal cortex, PLT - planum temporale, THL – thalamus.

3.7 Prediction of diagnostic group membership based on effective connectivity

We used the four connections, identified by one-way ANOVA as significantly different amongst the study groups, as independent variables in 6 different regression models to predict diagnostic group membership between study groups (Table 7). The overall percentage of correctly classified cases by each model ranged between 64.8 and 75.0%, which was substantially higher than the percentage attributable to chance in two-group prediction models (50%). The regression models classified patients better than healthy controls in all patient-control analyses. The best prediction of diagnostic group membership (75% correctly classified cases) was achieved in depressed patients with MDD and BD based on just one connection: from OFC to PRC. The regression models classified correctly 73.7% of patients with MDD and SCZ based on the connection from THL to PRC and the reciprocal connections between

PRC and OFC and 68.1% of patients with BD and SCZ based on the connection from THL to PRC and from PRC to OFC.

Table 7. Prediction of diagnostic group membership based on effective connectivity.

Comparison	**Connections left in the model[a]**			**Correctly classified cases (%)**		
		Wald	P*	By group		Overall
MDD vs HC	**HPC→ PLT**	4.31	0.038	MDD	HC	64.8
				84.8	33.3	
BD vs HC	**OFC → PRC**	4.93	0.026	BD	HC	72.7
	HPC→ PLT	5.46	0.019	73.9	71.4	
SCZ vs HC	**PRC→OFC**	5.33	0.021	SCZ	HC	71.1
	HPC→ PLT	4.35	0.037	79.2	61.9	
MDD vs BD	**OFC → PRC**	10.65	0.001	MDD	BD	75.0
				81.8	65.2	
MDD vs SCZ	**OFC → PRC**	3.62	0.057	MDD	SCZ	73.7
	THL → PRC	4.88	0.027	81.8	62.5	
	PRC→OFC	3.26	0.071			
BD vs SCZ	**THL → PRC**	5.68	0.017	BD	SCZ	68.1
	PRC→OFC	3.36	0.067	69.6	66.7	

[a]Binary logistic regression, backward elimination (Wald), *The significance values may be > 0.05 as they are based on fitting a single step, not a stepwise selection model, HC – healthy controls, MDD – major depressive disorder, BD – bipolar disorder, SCZ – schizophrenia, PRC - precuneus, HPC - hippocampus, OFC - orbitofrontal cortex, PLT - planum temporale, THL – thalamus.

4. Discussion

The main findings of the present transdiagnostic study point to differences in the reciprocal connections between the left orbitofrontal cortex and the left precuneus in major psychiatric disorders. The positive mean coupling values for the connection from the OFC to the PRC reflected an excitatory influence on bipolar patients, whereas the negative ones demonstrated an inhibitory effect on unipolar depression. The opposite connection from the left PRC to the left OFC was found to be significantly different between patients with SCZ and those with MDD as well as the HC but was significantly different from zero only in patients with SCZ (having a negative mean–inhibitory influence). In addition, the prediction model based on the OFC → PRC coupling values was able to discriminate between unipolar and bipolar depression with an overall accuracy of 75%. The significance of these findings will be discussed in the following lines.

Neuroimaging studies have implicated the role of OFC in several psychiatric disorders [25]. Structural changes, including gray matter volume (GMV) reduction, and sulco-gyral alterations, have been reported in first-episode and chronic SCZ and linked to aggressive behavior [26-28]. Similarly, in unipolar and bipolar depression studies have demonstrated state-dependent decreases of OFC GMV – evident only during a depressive episode and not during euthymia [29-31].

It is important to note that the orbitofrontal cortex has been suggested to have two distinct parts, with the medial OFC (mOFC) activated by rewarding and subjectively pleasant stimuli and the lateral OFC (lOFC) implicated in the effects of aversive and subjectively unpleasant stimuli, and in not receiving expected rewards or being punished [32,33]. MDD has been found to be characterized by reduced functional connectivity of the mOFC (Broadman area 13) with the parahippocampal gyrus and increased FC of the lOFC (Broadman area 47/12) with the precuneus, which is in line with the clinical manifestations of anhedonia (reduced anticipatory and consummatory pleasure) and the negative bias (increased negative affectivity including the negative sense of the self) [34]. Moreover, medicated patients demonstrated lower FC between lOFC and PRC compared to unmedicated patients, which suggests a possible "normalization" effect of treatment.

Notably, the orbitofrontal cortex ROI in the present study falls into Broadman area 47 and can be considered as part of the lateral OFC. Thus, our results support and expand the findings of Cheng et al. [34] by confirming the increased coupling between the lOFC and PRC and revealing the directionality of the disturbed connectivity, namely, an inhibitory connection from the lOFC towards the precuneus. In addition, we have been able to demonstrate that such increased connectivity characterizes bipolar depression as well but with an excitatory influence exerted by the lOFC on the precuneus.

Earlier neurotransmission hypotheses of depression focused mainly on monoamines, while more recent reports suggest a dysfunction of the glutamatergic neurotransmission as a possible mechanism as well [35]. Notably, at least two meta-analytic studies of magnetic resonance spectroscopy research suggest that Glx (a composite measure of glutamate and glutamine) levels measured in the prefrontal cortex of bipolar patients are increased [36,37]. In MDD, on the other hand, a meta-analysis by Arnone et a. confirmed a reduction in absolute values of the Glx in the prefrontal cortex [38]. Although highly speculative, the opposing patterns of glutamate dysfunction in bipolar and unipolar depression might serve as a possible explanation of the opposing influence of the OFC on the PRC found in our study groups. We can suggest that the increased glutamatergic neurotransmission in bipolar patients underlies the excitatory influence arising from the OFC, while in MDD the reduction in glutamate/glutamine levels is the base of the inhibitory influence exerted on the precuneus.

A possible interpretation of these findings might be found within the framework that postulates a division of the precuneus into an anterior region, involved in self-centered mental imagery strategies, and a posterior region, subserving successful episodic memory retrieval [39]. The PRC ROI in the present study falls within the anterior part. Thus the inhibitory effect in MDD might be linked to symptoms such as persistent low self-esteem in recovered unipolar patients which is not the case with bipolar depression where self-image is not different from healthy controls [40]. The excitatory influence of the OFC on the anterior PRC might represent the neurophysiological mechanism underlying the instability of self-image in bipolar depression [41].

On the other hand, the precuneus region, along with the neighboring posterior cingulate cortex (PCC), is considered a major hub of the Default Mode Network [42]. The DMN has been identified as one of the core resting-state networks that are "activated during internally focused tasks including autobiographical memory retrieval, envisioning the future, and conceiving the perspectives of others" [43]. Hyperactivity and hyperconnectivity of its nodes have been systematically identified in various psychopathological states, including SCZ and depression, and have been linked to increased self-referential thinking and ruminations, respectively [44].

Functional connectivity studies have identified both common and distinct disruptions in these major psychiatric disorders [45]. In SCZ the PRC/PCC node seems to be particularly affected with functional [46] as well as structural disturbances that have been linked to relevant genetic risk variants [47]. Similarly, in depression, the reduction of connectivity between PCC and bilateral superior parietal lobule (SPL) was identified, which is suggested to underly the balance between internally and externally focused attention [45]. This is in line with the clinical presentation and the suggested hypothesis of symptom formation in these two disorders – with a predominance of externalizing mental representations in SCZ leading to paranoid symptoms and overrepresented internalizing in depression that leads to self-defeating depressive symptoms.

The second major finding in the present study was the inhibitory influence of the PRC on the OFC that was detected in the group of SCZ patients but was not evident in the other three groups. This finding adds to and is in line with the disrupted connectivity theory of SCZ [48,49]. We might speculate that this inhibitory effect of the DMN on the reward processing system (OFC) can be linked to the clinical presentation of negative symptoms such as social withdrawal, anhedonia, apathy and lack of sensitivity to aversive stimuli [50]. In support of this interpretation are the findings of reduced structural connectivity (in terms of fractional anisotropy measures) of the left uncinate fasciculus, which connects lateral OFC with the temporal lobe in SCZ patients especially with negative symptoms [51].

Current SCZ theories suggest that the dysfunction of the neural reward system is related to negative and psychotic symptoms by disrupting reward processing and promoting context-independent false associations [52]. For optimal behavior and clear communication with the environment, efficient processing of reward and punishment information is essential. Some studies show that in SCZ this may be compromised, with patients having difficulty learning from incentive feedback [53]. Learning abnormalities may be associated with negative symptoms (e.g., anhedonia and social apathy) by altering the processing of rewarding experiences and with psychotic symptoms through facilitating abnormal associations [54]. Distorted coordination among brain circuits has been proposed as a key pathophysiological feature of SCZ, more specifically among the anticorrelated networks which underlie task activity and default modes [55].

At a molecular level the dopamine hypothesis is the most widely considered neurochemical hypothesis of schizophrenia. It postulates that symptoms of schizophrenia may result from increased dopaminergic neurotransmission in the basal ganglia and decreased dopaminergic neurotransmission in prefrontal brain regions, including the OFC. Recent alternative neurochemical models, however, involve glutamatergic mechanisms and particularly hypofunction of the N-methyl-D-aspartate (NMDA) receptors [56]. An increasing number of studies support the hypothesis of NMDAR hypofunction during development acting as a convergence point and leading to local gamma-aminobutyric acid (GABA) deficits and

input-output dysconnectivity in the prefrontal cortex, which eventually induces cognitive and social deficits [57].

In the present study, the predictive value of the disturbed OFC → PRC connectivity reached an overall accuracy of 75% in the discrimination between unipolar and bipolar depression. Keeping in mind that the distinction is based on a single parameter per subject (the A coupling value), this percentage is relatively high and comparable to the most recent reports of other similar studies, such as the 79% accuracy in MDD vs HC prediction based on FC [58]. To the best of our knowledge, the highest percentage of correct MDD vs BD classification based on resting-state fMRI (86%) has been achieved using a support vector machine approach [59].

Our study suffers from several limitations that need to be acknowledged. First, the sample size might not be sufficient to detect more subtle changes in connectivity with smaller effect size. Second, the medication status of the patient groups may have influenced the results since evidence of "normalization" of disturbed connectivity patterns following successful treatment has been reported [60]. Future research is needed to address those limitations by increasing the study sample and including non-medicated patients.

5. Conclusion

In conclusion, the present study has identified disturbed effective connectivity from the left lateral orbitofrontal cortex to the left anterior precuneus that differed significantly between unipolar depression, where the influence was inhibitory and bipolar depression, where the effect was excitatory. The inhibitory influence of the OFC (reward system) on the anterior PRC (self-centered mental imagery) might be linked to symptoms such as persistent low self-esteem in MDD, while the excitatory influence might represent the neurophysiological mechanism underlying the instability of self-image in BD [41](Knowles, Tai et al. 2007). In addition, an overall accuracy of 75% correct classification between the two diagnostic groups was achieved based solely on this connection.

The other prominent finding of the current study was the negative effective connectivity from the anterior PRC to the lateral OFC that was significantly different from zero only in the SCZ group and distinguished from HC and MDD patients. This inhibitory effect of the DMN (PRC) on the reward processing system (OFC) can be linked to the clinical presentation of negative symptoms such as social withdrawal, anhedonia, apathy and lack of sensitivity to aversive stimuli. Since the medication status may have influenced the results, future studies on unmedicated patients are needed to establish the replicability of our findings.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The Ethics Committee at the Medical University of Plovdiv has approved the protocol of the study on 29 May 2015 (ID: P-396/29.05.2015).

HUMAN AND ANIMAL RIGHTS

No animals were used in the study. The reported experiments on humans were in accordance with the ethical standards of the committee responsible for human experimentation (institutional and national), and with the Helsinki Declaration of 1975, as revised in 2013 (http://ethics.iit.edu/ecodes/node/3931).

CONSENT FOR PUBLICATION

Prior to inclusion, each of the participants provided written informed consent.

AVAILABILITY OF DATA AND MATERIALS

Data and materials are available upon request.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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