 doi:10.20944/preprints202012.0031.v1

Original paper

DIAGNOSTIC TASK SPECIFIC ACTIVATIONS IN FUNCTIONOAL MRI AND ABERRANT CONNECTIVITY OF INSULA WITH MIDDLE FRONTAL GYRUS CAN INFORM THE DIFFERENTIAL DIAGNOSIS OF PSYCHOSIS

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Abstract: We constructed a novel design integrating the administration of a clinical self-assessment scale with simultaneous acquisition of functional Magnetic Resonance Imaging (fMRI), aiming at cross-validation between psychopathology evaluation and neuroimaging techniques. We hypothesized that areas demonstrating differential activation in two groups of patients (paranoid and depressive) will have distinct connectivity patterns and structural differences.

51 patients with a paranoid (n=25) or depressive (n=26) syndrome were scanned with 3 different MRI sequences: a structural and two functional sequences – resting-state and task-related fMRI (the stimuli represent items from a paranoid-depressive self-evaluation scale).

We managed to separate the two clinical entities by identifying two significant clusters of activations in the paranoid group – the left Precuneus (PreCu) extending to the left Posterior Cingulate Cortex (PCC) and the right Angular Gyrus (AG). In paranoid patients, the connectivity of the middle frontal gyrus (MFG), a part of the Dorsolateral Prefrontal Cortex (DLPFC) to the Anterior Insula (AI) demonstrated a significant difference between the two groups. The observed activations of PreCu, PCC and AG (involved in the Default Mode Network DMN) might be indirect evidence of the inhibitory connection from the DLPFC to AI, interfering with the balancing function of the insula as the dynamic switch in the DMN.

The results from our study support the translational cross-validation of a clinical psychological assessment tool (von Zerssen's Paranoid-Depressive Scale) by means of functional MRI. At this stage, we can confirm the sensitivity of the method (its ability to differentiate healthy controls from patients), as well as its specificity (distinction between different psychopathological conditions – in the case of our study - paranoid vs. depressive syndrome).

Keywords: neuropsychiatric disorders, translational neuroscience, neuroimaging, brain networks, connectivity, schizophrenia, depression, precuneus, insula, frontal cortex, default mode network

 doi:10.20944/preprints202012.0031.v1

1. Introduction

One of the most common debates in psychiatry appears to be the fact that diagnosis and treatment decisions rely mainly on patient reports, behavioral observation, and the willingness to make judgments about the underlying inner nature of the patient's experience, rather than to observe accurate objective biomarkers. The field of psychiatry needs to incorporate a trans-disciplinary approach towards the diagnosis in order to establish a biological cross-validation of clinical phenomenology, which has been missing since its differentiation as an independent medical specialty.

The current diagnostic systems in psychiatry (such as the International Classification of Diseases (ICD) (1) and the Diagnostic and Statistical Manual (DSM) of Mental Disorders (2) are widely used among clinicians although they have low validity (3). This is evident from the fact that the diagnostic process is hampered by certain obstacles such as: heterogeneity, comorbidity, unclear distinctions between normal and pathological behavior. Another important issue is that mental disorders are classified based exclusively on clinical characteristics, without considering the etiological factors (4). Translational neuroscience may be the key to establishing fundamental knowledge about the origin of behavioral disorders by identifying and explaining the underlying neurobiological correlates of psychiatric conditions. Neuroimaging techniques, such as functional Magnetic Resonance Imaging (fMRI), offer the possibility for translation between basic neuroscience and pathological behavioral manifestations that correlate with it. The integration of neuroimaging methods and the hitherto acquired know-how of the underlying genetic causes, neurochemical dysfunctions, and neuroinflammatory mechanisms may finally allow a change of the current status of psychiatry (5) and the establishment of evidence-based explanations of the etiology of mental disorders.

In recent decades, many studies have been conducted with the aim to detect structural and functional abnormalities in psychiatric disorders. Despite years of efforts in this area, however, the results remain inconsistent (6). This may be partly due to the specificity of the design of the methods used. Common practice in fMRI studies is to conduct a pre- and post-scan clinical assessment. This causes a time difference between the two measurements. In certain situations, this could affect the accuracy of the findings (e.g., in bipolar patients with rapid cycling) (7). To address this issue, it could be beneficial to create or transform some of the current assessment or self-assessment questionnaires via cross-validation against certain neurobiological biomarkers. FMRI could serve as the appropriate support element for an evidence-based design, where the gathered neuroimaging data, together with the parallel implementation of a self-assessment scale (8), could construct a scientifically valid instrument that can be used by clinicians in daily practice with trust in the reliability of the method. Therefore, when using this translational approach, which incorporates fundamental neuroscience, neuroimaging technologies, psychometric instruments and psychopathology,

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physicians can rely on an accessible and valid diagnostic tool (9). The initiative might have an effect not only on the diagnostics, but also on the prevention, treatment, and monitoring of the therapeutic effect, as well as the decision regarding the choice of medications.

As a scientific effort on the application of the translational model in psychiatry, our research group has performed several experiments. We designed a novel paradigm, which integrates clinical self-assessment scale administered simultaneously with the acquisition of fMRI, aiming at cross-validation between psychopathology evaluation and neuroimaging techniques (4,7,10). Our research has been conducted in three phases. The first study was designed to integrate the clinical self-assessment scale of von Zerssen (11) administered concurrently with fMRI. We used two conditions during the first phase of the research: diagnostically specific (DS) items applying the depression scale and diagnostically neutral (DN) applying the scale of general interests performed in block design, contrasting the results between patients, suffering from depressive episode and healthy controls. Thus, we were able to detect distinct activations in the depressed group while processing the DS items that were not present in the control group thus demonstrating the sensitivity of the test (7). During the second phase of the research, we upgraded the paradigm by including one more condition (namely the paranoia items from the paranoid-depressive scale – PS) and we recruited patients with paranoid syndrome in the context of Schizophrenia to explore the comparison between the different nosological groups (e.g., the specificity of the test). However, no residual activations were produced in the direct comparison between the two patient groups which led us to the next level of our experiments.

At the final stage we applied multivariate analysis to the same dataset, the goal being to implement an unsupervised machine learning approach, where the brain signatures identified would correlate to the different conditions used in the design. By using a multivariate linear model (MLM) and principal component analysis, we were able to differentiate the two psychiatric groups - paranoia and depression. Three brain patterns were established following the individual and group MLM, summarizing all the individual variability of the individual brain patterns. The aforementioned objective of establishing a translationally valid tool in the diagnostic process of schizophrenia and affective disorders is supported by this finding.

In this context, the aim of the present study was to advance the translational approach used so far by combining data already acquired from different modalities namely high-resolution structural images, resting state, and task-related data. Since in our pilot study the sample size was relatively small, which might have led to the negative results of the direct comparison between the groups when stringent criteria for statistical significance were applied, we hypothesized that increasing the sample would enable us to overcome this issue. In addition, our goal was to explore whether the differences in the brain activations during

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the task can be translated in or explained by some structural or connectivity changes as well. In order to achieve this, we used voxel-based morphometry analysis to assess the gray matter volumes and spectral dynamic causal modeling to derive the effective connectivity measures of eight specific regions of interest. We hypothesized that the areas demonstrating differential activation in the two groups will simultaneously have distinct connectivity patterns and structural differences.

2. Materials and Methods

2.1 Participants

For the current study we have recruited 51 patients with a current psychotic episode - in the context of schizophrenia (n=25, mean age 38.8 ± 13.5 y, 13 males), or depressive episode (n=26, mean age 41 ± 11.4 y, 9 males) - in the context of major depressive disorder (n=10, mean age 37.5 ± 9.9 y, 4 males) or bipolar disorder (n=16, mean age 43.1 ± 12.1 y, 5 males). The assessment of the participants was performed by experienced psychiatrists (D.S., S.K., K. A.) using the general clinical interview and the structured Mini International Neuropsychiatric Interview (M.I.N.I 6.0) (12) and Clinical Global Impression (CGI) scale (13) as well as the Montgomery–Åsberg Depression Rating Scale (MADRS) (14) and the Positive and Negative Syndrome Scale (PANSS) (15). Depressed patients with a total MADRS score of at least 20 were included as well as psychotic patients with at least 3 on P1 (delusions) or P6 (suspiciousness) PANSS. Both clinical groups were on stable medication during the past 14 days.

The exclusion criteria were the following - age under the age of 18 or over the age of 65, presence of metal implants or body grafts (e.g., pacemaker) incompatible with MRI, comorbid mental disorder, (e.g., substance or alcohol use disorder, obsessive compulsive disorder, etc.), severe somatic or neurological disease, and traumatic brain injury with loss of consciousness. All subjects gave their informed consent for inclusion before they participated in the study. The study was conducted in accordance with the Declaration of Helsinki. The protocol of the study was approved by the University's Ethics Committee (ID: P-369/29.05.2015).

2.2 Image acquisition

The participants were scanned on a 3T MRI system (GE Discovery 750w) with 3 different MRI sequences: high resolution structural scan (Sag 3D T1 FSPGR sequence), with slice thickness 1 mm, matrix 256x256, TR (relaxation time) 7.2 msec, TE (echo time) 2.3,

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and flip angle 12°, and two functional scans (2D EPI sequence) while resting with eyes closed - slice thickness 3 mm, 36 slices, matrix 64x64, TR - 2000 msec, TE – 30 msec, flip angle 90°, 192 volumes and during the task (see following paragraph) - slice thickness 3 mm, matrix 64x64, TR 2000 msec, TE 30 msec, and flip angle 90°, 256 volumes. The functional scan started with 5 dummy time series which were automatically excluded.

2.3 fMRI task

The paradigm was created using E-prime software (Psychology Software Tools, Inc) and consisted of 32 s blocks with three different active conditions and one 20 s block with the rest condition (fixation cross). The stimuli were presented using Nordic Neuro Lab Visual System. As it is described in detail in our previous work (10,16) we will here briefly summarize it.

The active blocks represented four written statements of 8 s each taken from the von Zerssen paranoia-depression scale. There were Depression Specific (DS) blocks with the statements from depression subscale (“I often feel simply miserable”, “I don’t have any feelings anymore”), and Paranoid Specific (PS) blocks from the paranoia subscale (”Other people constantly follow and control me”). The Diagnostically Neutral (DN) blocks included statements from a questionnaire about general interests and likes (such as “I like to write books or plays”, “I like to repair household appliances”, etc.). Four possible answers (“completely true”, “mostly true”, “somewhat true”, “not true”) and the respective four response buttons (upper left, lower left, lower right, upper right) were presented under each statement. The whole task incorporated four blocks of each type, alternating between the three active conditions, and followed by the rest condition (DS__rest__DN__rest__PS__rest…). The participants were instructed to read the statements carefully and to respond with a button press according to their level of agreement. During the rest condition they had to focus on the fixation cross without thinking of anything.

2.4 MRI data analysis

2.4.1 Structural data analysis - voxel based morphometry

The analysis of the MRI images was performed using the SPM 12 (Statistical Parametric Mapping, http://www.fil.ion.ucl.ac.uk/spm/) software running on MATLAB R2020 for Windows and the CAT 12 toolbox implemented in SPM (http://www.neuro.uni-jena.de/software/). The preprocessing of the T1 images encompassed first - segmentation with the CAT 12 toolbox, including normalization to standardized MNI space, and second - spatial smoothing with an 8 mm (FWHM) Gaussian kernel. In addition, the total intracranial volume (TIV) was calculated for each subject. In the next step a general-linear model was defined with the age, sex, and TIV as covariates. We then compared the grey-matter volumes

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of the two groups with a two-sample t-test. The statistical threshold was set to $p<0.05$ FWE (Family Wise Error) corrected.

2.4.2 Task-related functional data analysis

The functional images (both from the task and from the resting state scans) were first realigned for correction of head motion, co-registered with the high-resolution anatomical image, normalized to MNI (Montreal Neurological Institute) space, and spatially smoothed with an 8 mm full-width-at-half-maximum (FWHM) Gaussian kernel.

Following the preprocessing a first-level analysis was conducted using a general linear model (GLM) applied to the time series, convolved with a canonical hemodynamic response function. Covariates of no interest included the six rigid body motion correction parameters. Individual T-contrasts were defined for the active vs passive conditions. The contrast maps obtained from each comparison were included in a second-level random-effects analysis to test for differences between the two patient groups (schizophrenia>depression=SCH>D and depression>schizophrenia=D>SCH). The level of significance was set to $p<0.05$ FWE corrected using an uncorrected cluster-forming threshold of $p<0.001$. The effects of age and sex were controlled for as they were added as covariates of no interest in the design matrix.

2.4.3 Resting state data analysis - effective connectivity

Following the preprocessing (same as for the task-related data), first-level resting state analysis was conducted using a general linear model (GLM) applied to the time series. Nuisance covariates included the six rigid body motion parameters, average white matter and cerebrospinal fluid signal time series. BOLD timeseries were extracted for eight predefined regions of interest of 6 mm radius spheres (3 mm radius for angular gyrus and planum temporale). These were the following left hemisphere regions with their MNI coordinates: precuneus (PreCu) [-10, -64, 24], hippocampus (HPC) [-24, -11, -18], anterior insula (AI) [-34, 22, 4], angular gyrus (AngG) [-26, -80, 42], orbitofrontal cortex (OFC) [-40, 27 -8], planum temporale (PlT) [-54, -33, 15], thalamus (anterior nuclei) (Th) [-6, -10, 2], middle frontal gyrus (MFG) [-41, 19, 41]. BOLD signal from some of the ROIs (OFC) was lacking in one patient which led to the exclusion of this dataset from further analysis.

Spectral dynamic causal modelling (spDCM) was performed with these eight regions of interest. We used a fully connected model where each node was connected to each other node. Further, the individual spDCM models were 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 statistical analysis in SPSS was performed.

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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 were performed by means of SPSS 22.0 for Windows. The level of significance was set to $p < 0.05$ for all tests. Student's t-test was employed for continuous variables and Chi-square test - for categorical ones.

3. Results

3.1 Demographic and clinical characteristics

There were no statistically significant differences in age, sex and education level between paranoid and depressed patients. The clinical characteristics of the patient samples are given in detail in Table 1. The two depressed patients' subgroups (e.g., bipolar and unipolar) did not differ significantly in their demographic or clinical variables – see Table 2.

Table 1. Demographic and clinical characteristics of all participants

	Schizophrenia patients (n=25)	**Depressed patients** (n=26)	**Statistical significance**
Age (mean ± SD)	38.8 ± 13.5	41 ± 11.4	0.434a
Sex (M/F)	13/12	9/17	0.210b
Education (years)	13.4 ± 3	13.6 ± 3.3	0.567a
Age at onset (years)	26 ± 9.2	29.6 ± 10.3	0.173a
Illness duration (months)	150 ± 115	139 ± 92	0.885a
Episode duration (weeks)	20.3 ± 28.4	12.6 ± 16	0.141a

SD – Standard Deviation, [a] Independent samples t-test, [b] χ^2 - test, * $p<0.05$.

Table 2. Demographic and clinical characteristics of the two depression subgroups

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	MDD patients (n=10)	BD patients (n=16)	Statistical significance
Age (mean ± SD)	37.5 ± 9.9	43.1 ± 12.1	0.286[a]
Sex (M/F)	4/6	5/11	0.648[b]
Education (years ± SD)	16 ± 3.7	12.6 ± 2.6	0.113[a]
MADRS score (mean ± SD)	27.4 ± 4.7	30.4 ± 6.7	0.357[a]
Age at onset (years)	27.2 ± 6.4	31 ± 12	0.522 [a]
Illness duration (months)	129.2 ± 98.5	144.3 ± 91.3	0.803[a]
Episode duration (weeks)	10.4 ± 11.2	13.7 ± 18.5	0.490[a]

SD – Standard Deviation, [a] Independent samples t-test, [b] χ^2 - test, MADRS - Montgomery–Åsberg Depression Rating Scale, * p<0.05, N – number of patients, MDD – major depressive disorder, BD – bipolar disorder.

3.2 Voxel-based morphometry analysis

The gray matter volumes of the two patient groups failed to demonstrate any significant differences when the effects of age, sex and TIV were accounted for and a stringent statistical threshold of p<0,05 after FWE correction was applied.

3.3 Task related data analysis

The comparison between the schizophrenia and the depression group (schizophrenia>depression) using a t-test on the contrasts between the DP and the PS blocks resulted in two significant clusters of activations on both cluster and peak level. The first one was localized in the left precuneus extending to the left posterior cingulate gyrus with a cluster size of 376 voxels, and a level of significance p = 0.034, peak MNI coordinates [-12, -60, 30]. The second cluster with a size of 72 voxels, encompassed regions of the right superior parietal lobule, and right angular gyrus, p=0.023, peak MNI coordinates [30, -50, 36]. An illustration of these results is given in Figure1. The opposite comparison (depression>schizophrenia) did not yield any significant clusters.

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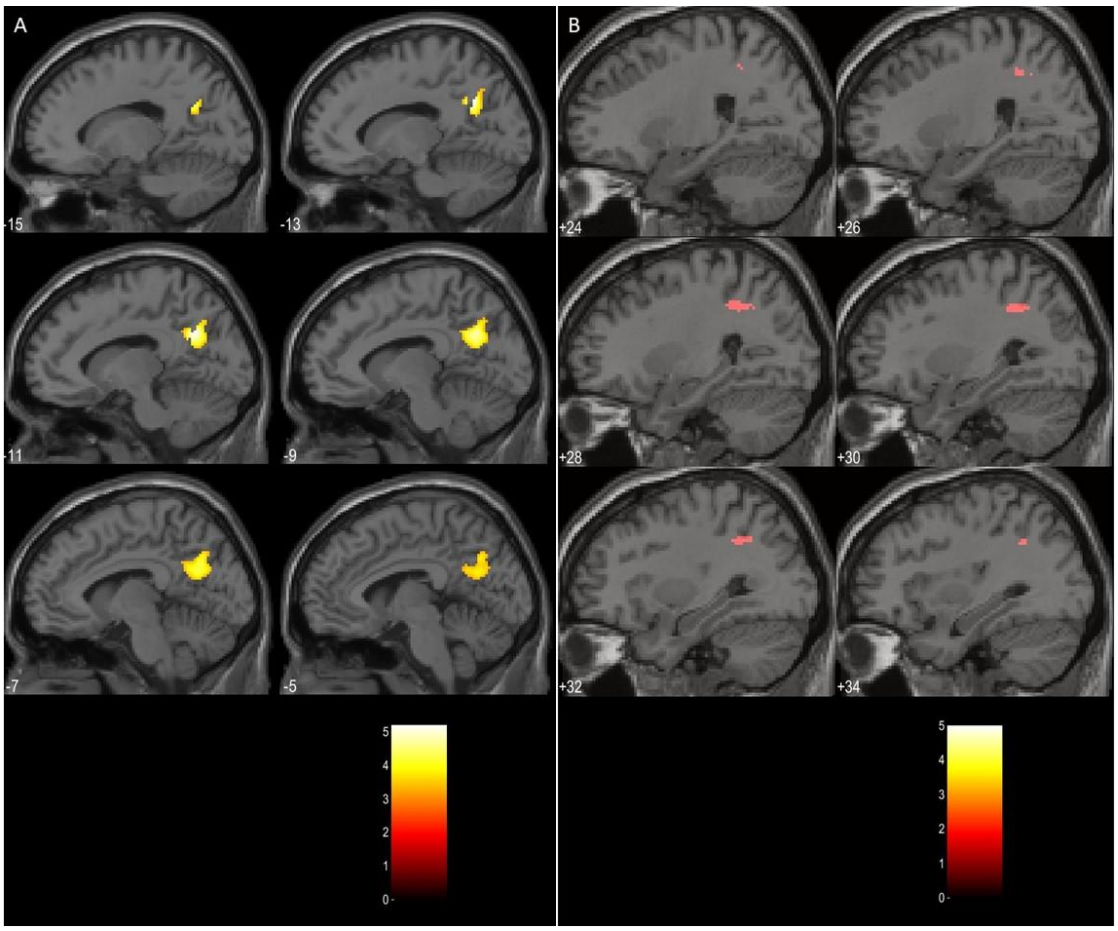
Figure 1. Clusters of activations significantly higher in schizophrenia (A – left precuneus B – right posterior parietal lobule)



3.4 Effective connectivity analysis

3.4.1 *Effective connectivity in the sample*

One sample t-test was employed to identify the connections that were significantly different from zero in the whole sample e.g., both groups. As it can be seen in Table 3, all eight nodes had some significant connections, but the most frequently involved ones were precuneus, anterior insula, hippocampus, and orbitofrontal cortex with 3 to 5 such connections. The other three regions - planum temporale, thalamus and middle frontal gyrus had only 2 significant connections with the other nodes. In addition, each of the nodes except for the thalamus demonstrated significant self-inhibitory connections.

Table 3. Connections significantly different from zero in the whole sample

Connections	Mean	SD	[a] Significance
PreCu ⊃	-0.133	0.290	0.002

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OFC → PreCu	0.094	0.334	0.027
HPC ⊃	-0.091	0.240	0.009
PreCu → AI	-0.151	0.328	0.002
HPC → AI	-0.128	0.354	0.013
AI ⊃	-0.159	0.226	0.000**
PreCu → AngG	0.154	0.420	0.013
AngG⊃	-0.160	0.301	0.000**
Th → AngG	-0.117	0.348	0.021
HPC → OFC	-0.120	0.316	0.010
AI → OFC	0.186	0.335	0.000**
OFC⊃	-0.086	0.293	0.041
AI → PlT	0.152	0.292	0.001
AngG → PlT	0.088	0.293	0.015
PlT⊃	-0.182	0.216	0.000**
HPC → Th	0.080	0.276	0.045
HPC → MFG	-0.180	0.333	0.000**
Th → MFG	-0.118	0.345	0.019
MFG ⊃	-0.220	0.271	0.000**

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

3.4.2 *Effective connectivity in the paranoid group*

In the paranoid group the connections that were found to be significantly different from zero included mainly the angular gyrus, anterior insula and planum temporale. Significant self-inhibitory connections presented the following nodes – precuneus, angular gyrus, planum temporale and thalamus. These results are given in details in Table 4.

Table 4. Connections significantly different from zero in the paranoid group

Connections	Mean	SD	[a] Significance
PreCu ⊃	-0.156	0.263	0.008
AI ⊃	-0.108	0.207	0.017

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MFG → AI	-0.112	0.257	0.043
AngG⊃	-0.161	0.300	0.015
Th → AngG	-0.199	0.337	0.011
AI → OFC	0.169	0.256	0.004
AngG → PlT	0.120	0.265	0.037
PlT⊃	-0.214	0.230	0.000**
PlT → Th	-0.156	0.324	0.035
Th ⊃	-0.258	0.328	0.000**

SD – Standard Deviation, [a] One sample t-test $p<0.05$, ** $p < 0.001$, ⊃ - self-inhibitory connection,

PreCu - precuneus, HPC - hippocampus, AI - anterior insula, AngG - angular gyrus, OFC - orbitofrontal cortex, PlT - planum temporale, Th – thalamus, MFG - middle frontal gyrus.

3.4.3 *Effective connectivity in the depressed group*

The connections that were identified in the depression group involved primarily the anterior insula, orbitofrontal cortex, and hippocampus. The self-inhibitory connections were significantly different from zero for the above-mentioned three regions, the middle frontal gyrus and the angular gyrus as well. The coupling strengths are detailed in Table 5.

Table 5. Connections significantly different from zero in the depressed group

Connections	Mean	SD	[a] Significance
HPC ⊃	-0.145	0.270	0.011
PreCu → AI	-0.200	0.300	0.002
HPC → AI	-0.198	0.292	0.002
AI ⊃	-0.207	0.236	0.000**
AngG⊃	-0.161	0.310	0.014
HPC → OFC	-0.173	0.289	0.005
AI → OFC	0.202	0.400	0.016
OFC⊃	-0.140	0.241	0.007
AI → PlT	0.208	0.311	0.002
PlT⊃	-0.154	0.204	0.001
HPC → MFG	-0.255	0.357	0.001

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MFG ⊃	-0.186	0.209	0.000**

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

3.4.4 Differences between paranoid and depressed patients

In order to explore the differences between the two groups, independent samples t-tests comparing the mean connectivity strengths were performed. The coupling strengths of the connection from the middle frontal gyrus to the anterior insula demonstrated significant difference between the two groups ($p=0.041$) with the depressed patients having positive mean values (0.054± 0.300) but not significantly different from zero (see Table 5) and the paranoid patients having negative mean values (-0.112± 0.257) that were significantly different from zero (see Table 4). An illustration of these results is presented in Figure 2.

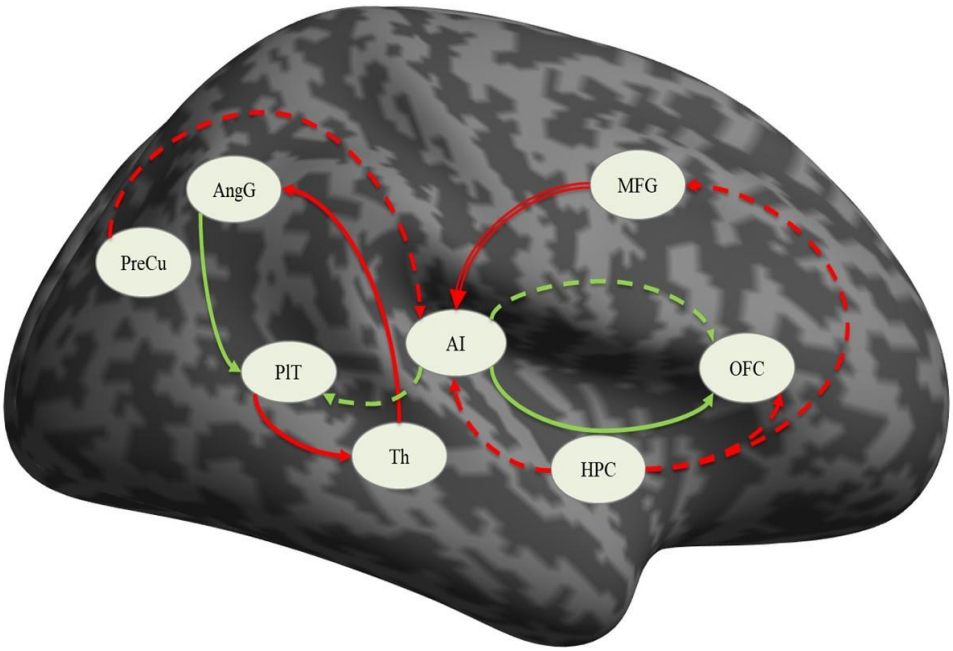

Figure 2. Connections significantly different from zero - solid line – schizophrenia, dashed line – in depression, green - excitatory, red – inhibitory, double red line – significantly different between the groups. PreCu - precuneus, HPC - hippocampus, AI - anterior insula, AngG - angular gyrus, OFC - orbitofrontal cortex, PlT - planum temporale, Th – thalamus, MFG - middle frontal gyrus.

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4. Discussion

The results of the present study on paranoid and depressed patients can be summarized as follows: i) there were no significant structural differences between the groups in terms of gray matter volumes on a whole brain voxel-by-voxel comparison, ii) the paranoid group demonstrated significantly more activation in the left precuneus, left posterior cingulate gyrus as well as the right superior parietal lobule and angular gyrus during the processing of the paranoid items of the von Zerssen scale when contrasted with the depression items, iii) the connection from the middle frontal gyrus to the anterior insula was the only significantly different in the direct comparison between the groups, although several other connections at group level seemed to be different as well. The significance of these findings will be discussed in the following lines.

Structural changes as evident in GM volume reductions of different brain regions have been found in schizophrenia and in depression when compared to healthy controls (17–19). However, studies directly comparing the two groups are scarce. In the recent years, there is an increasing number of articles identifying the fronto-temporal regions, insula and thalamus as more impaired in schizophrenia than in bipolar disorder (20). On the other hand, the study of Shao et al. did not find significant GM differences between schizophrenia and depression (21). Thus, the negative results of our study concerning the VBM analysis may be due to the heterogeneity of the depression sample which included both bipolar and unipolar patients.

The results of the task related data analysis implicated mainly the role of the left precuneus, left posterior cingulate cortex (PCC) and right angular gyrus. The PCC is a central node in the brain default mode network (DMN) and has strong metabolic activity and strong structural connectivity to multiple brain regions, indicating that it plays a role as a cortical hub (22). Along with the precuneus, it is considered to be involved in autobiographical memory processing (23). Structural and functional disturbances in the PCC occur in a number of neurological and psychiatric conditions, including neurodegenerative diseases (24), autism spectrum disorder (25), attention deficit hyperactivity disorder (26) and schizophrenia (27).

It is considered that the left precuneus participates, along with the left prefrontal cortex, in the recollection of episodic memories (28), notably those referring to the self (29). It is also activated when a third-person versus first-person point of view is taken (30). Along with the superior frontal gyrus and orbitofrontal cortex, the precuneus is activated as individuals render decisions that require to behave out of empathy and to forgive (31). Thus, we can speculate that the increased activation of this region in the schizophrenia group during

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the processing of the paranoid items in contrast to the depressive items is compatible with the hypothesis of stronger involvement of their autobiographical memory.

The right angular gyrus (AngG) belongs to the inferior parietal lobule and is part of the Default Mode Network (32). The AngG serves as a bridge where interconnected sensory input is merged and integrated to understand and give context to events, exploit mental representations, redirect attention to the specific information and focus on solving relevant problems. It is also involved in social cognition and semantic processing as well as in memory retrieval (33). In schizophrenia where aberrant modulation/activation of the right angular gyrus has been observed (34), it was also correlated with reverse asymmetry in this area (35). The more significant involvement of this region in schizophrenic patients is most likely related to the specificity of the task e.g., processing of the relevant paranoid items.

Our analysis of the resting state fMRI data has demonstrated that in schizophrenic patients significant effective connectivity i.e. causal interaction in terms of excitatory influence is exerted by the Anterior Insula (AI) on the OrbitoFrontal Cortex (OFC) and by the Angular Gyrus (AngG) on the Planum Temporale (PlT), whereas inhibitory influences are exerted by the Middle Frontal Gyrus (MFG) on the AI, by the Thalamus (anterior nuclei) on the AngG and by Planum Temporale on the Thalamus. In the patients suffering from a depressive episode significant excitatory influence is exerted by AI to OFC and to PlT, while inhibitory influences are exerted by PreC and HPC to AI, by HPC to AI, by HPC to OFC and by HPC to MFG.

However, the comparison between the two groups resulted in one significant connection – the inhibitory influence of the MFG on the AI, which was significantly different from zero only in the schizophrenic group, thereby indicating impaired connectivity between the frontal cortex and the insular cortex. This particular area of the MFG is a part of the Dorsolateral Prefrontal Cortex (DLPFC) and is implicated in the pathophysiology of several neuropsychiatric illnesses (36). It is among the most recently developed regions of the human brain in terms of evolution and its maturation continues up until adulthood. The functions that are linked to the DLPFC include sensory feedback, retention in short-term memory, and motor signaling (37). In addition, the DLPFC is engaged in the decision-making process, including moral decisions as well as risk evaluation (38). This region is known to be involved in executive functions - cognitive processes such as working memory, cognitive resilience (39), and long-term planning (40). It is hypothesized that the DLPFC may also be engaged in the act of deception and lying, which is assumed to inhibit the natural propensity to say the truth (41).

 doi:10.20944/preprints202012.0031.v1

The dorsolateral prefrontal cortex dysfunction model of cognitive deficits in schizophrenia is supported by the present research. In addition, the identified effects of the connectivity to the anterior insula offer new insights into how dorsolateral prefrontal cortex dysfunction may contribute to the impairment of cognitive functions, behavioral disorganization, and functional disability in people suffering from schizophrenia. We propose a pathophysiological model in which cognitive impairment is present due to the inability to recruit and sustain an organized network between the frontal and insular cortex (42).

In a previous study conducted by our team, Kandilarova et al. (43) we found that depressed patients had a significant reduction in the strength of the right-sided connection from the AI to the MFG as well as significant excitatory connection between the amygdala and the anterior insula compared to healthy controls. Because both the Salience Network and the ventral Frontoparietal Network have nodes located in the anterior insular cortex (44) and the fact that some authors accept this high degree of correlation between the two networks as evidence that it was only one network (45), we have proposed that our findings add to this evidence by showing the directionality of this disrupted connectivity namely from the insular cortex to the DLP in depressive episode. However, the connection from the MFG to the AI in this previous study was found not to be significantly different than zero in both healthy controls and depressed patients which is the case in the present study as well.

The findings of our current study suggest that the connectivity from DLPFC to the anterior insula can be interpreted as evidence for the presence of an aberrant network that leads to behavioral abnormalities, the manifestation of which depends on the direction of influence. The effective connectivity from the anterior insula to the DLPFC is manifested as depressive symptoms, and the inhibitory effect from the DLPFC to the anterior insula is reflected in the paranoid symptoms of schizophrenia. This suggests that the two psychiatric conditions share common neural network that is disrupted but the clinical features depend on the direction of the inhibition and the followed mechanisms from these connectivity disruptions.

In our previous study (43) we speculated that a disruption of the influence of the AI on the Default Mode Network and the Executive Network (as it was the case with our sample of depressed patients) may this could lead to a prevalence of hyperactivity of the DMN. In the current study we can suggest that the observed inhibitory connection from the DLPFC to AI in patients with schizophrenia might interfere with the balancing function of the insula of the dynamic switch between the DMN. An indirect evidence for that might be the observed

 doi:10.20944/preprints202012.0031.v1

activation of both precuneus and posterior cingulate (involved in the DMN) in patients with schizophrenia during the task related fMRI session of the current study.

In conclusion, we can state that the results from our study support the translational cross-validation of the clinical psychological assessment (von Zerssen's Paranoid-Depressive Scale) by means of functional MRI, where the blocks of visual stimuli represent contrasting items from the clinical scales. At this stage, we can confirm not only the sensitivity of the method (its ability to differentiate healthy controls from patients), but we can also confirm its specificity (distinction between different psychopathological conditions – in the case of our study - paranoid vs. depressive syndrome). This methodology can potentially promote the subsequent re-validation of psychiatric classifications and assessment methods based on more reliable evidence-based neurobiological markers.

Moreover, the results from the task-related analysis (residual activations in the Precuneus, the Posterior Cingulate Cortex and the Angular Gyrus) and the disrupted resting state connectivity from the Dorsolateral Prefrontal Cortex (Middle Frontal Gyrus) to the Anterior Insular Cortex observed in the paranoid group indicate the involvement of neural networks such as the Salience Network and the Default Mode Network and their abnormal interactions with each other in schizophrenia etiology. However, the exact mechanisms that navigate those interactions are not fully understood and need further investigation in the future.

The limitations of our study refer to the heterogeneity of the sample and the innovative design of our paradigm, which leads to difficulty in attempting to correlate the findings with other similar studies. Those limitations could be addressed by extending translational neuroimaging research using a similar approach to the detection of the functional MRI substrate corresponding with the clinical self-assessment tools in replication protocols across independent centers. In order to have more precise results in the future we need to focus on integrating the knowledge gained not only by single modalities of MRI, but also by comparing and integrating the results from task-based fMRI with the residual whole brain activations observed during the resting state fMRI, as well as the data from the structural MRI.

Author Contributions: For research articles with several authors, a short paragraph specifying their individual contributions must be provided. The following statements should be used “Conceptualization, DS; methodology, DS and SK; validation, KA and SK.; formal analysis RP.; investigation KA and DS; resources KA, ZA and DS.; data curation, SK and DS.; writing—original draft preparation: KA, SK, DS.; writing—review and editing, DS and AT.; visualization, RP; supervision, SB and SK.; project administration, SK; funding acquisition, SK. All authors have read and agreed to the

published version of the manuscript. please turn to the CRediT taxonomy for the term explanation. Authorship must be limited to those who have contributed substantially to the work reported.

Funding: Please add: "This research received no external funding" or "This research was funded by MEDICAL UNIVERSITY OF PLOVDIV". Check carefully that the details given are accurate and use the standard spelling of funding agency names at https://search.crossref.org/funding, any errors may affect your future funding.

Acknowledgments: In this section you can acknowledge any support given which is not covered by the author contribution or funding sections. This may include administrative and technical support, or donations in kind (e.g., materials used for experiments).

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Americans N, Article S, Haghir H, Mokhber N, Azarpazhooh MR, Haghighi MB, et al. The ICD-10 Classification of Mental and Behavioural Disorders. IACAPAP e-Textbook of child and adolescent Mental health. 2013;55(1993):135–139.

2. Wakefield JC. DSM-5: An Overview of Changes and Controversies. Vol. 41, Clinical Social Work Journal. 2013. 139–154 p.

3. Brunoni AR. Beyond the DSM: Trends in psychiatry diagnoses [Internet]. Vol. 44, Revista de Psiquiatria Clinica. Universidade de Sao Paulo; 2017. 154–158 p. Available from: http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0101-60832017000600154&lng=en&nrm=iso&tlng=en http://www.scielo.br/scielo.php?script=sci_abstract&pid=S0101-60832017000600154&lng=en&nrm=iso&tlng=en

4. Stoyanov D, Kandilarova S, Paunova R, Barranco Garcia J, Latypova A, Kherif F. Cross-Validation of Functional MRI and Paranoid-Depressive Scale: Results From Multivariate Analysis. Front Psychiatry [Internet]. 2019 [cited 2020 Nov 3];10. Available from: https://www.frontiersin.org/articles/10.3389/fpsyt.2019.00869/full

5. Todeva-Radneva A, Paunova R, Kandilarova S, St. Stoyanov D. The Value of Neuroimaging Techniques in the Translation and Transdiagnostic Validation of Psychiatric Diagnoses - Selective Review. Current Topics in Medicinal Chemistry. 2020;20(7):540–553.

6. Specht K. Current Challenges in Translational and Clinical fMRI and Future Directions. Front Psychiatry [Internet]. 2020 [cited 2020 Oct 20];10. Available from: https://www.frontiersin.org/articles/10.3389/fpsyt.2019.00924/full

7. Stoyanov D, Kandilarova S, Borgwardt S, Stieglitz R-D, Hugdahl K, Kostianev S. Psychopathology Assessment Methods Revisited: On Translational Cross-Validation of Clinical Self-Evaluation Scale and fMRI. Front Psychiatry [Internet]. 2018 [cited

2020 Nov 3];9. Available from: https://www.frontiersin.org/articles/10.3389/fpsyt.2018.00021/full

8. Stoyanov DS. AS09-02 - Translational cross-validation among neuroscience and psychiatry: prospects for diagnostic assessment and psychopharmacology. European Psychiatry. 2012 Jan 1;27:1.

9. Aryutova K, Kandilarova S, Todeva-Radneva A, Stoyanov D. Clinical Use of Neurophysiological Biomarkers and Self-Assessment Scales to Predict and Monitor Treatment Response for Psychotic and Affective disorders. Current Pharmaceutical Design. IN PRESS;

10. Stoyanov D, Kandilarova S, Arabadzhiev Z, Paunova R, Schmidt A, Borgwardt S. Cross-Validation of Paranoid-Depressive Scale and Functional MRI: New Paradigm for Neuroscience Informed Clinical Psychopathology. Front Psychiatry [Internet]. 2019 [cited 2020 Nov 3];10. Available from: https://www.frontiersin.org/articles/10.3389/fpsyt.2019.00711/full

11. Zerssen DV. Assessment of depression. 1986;

12. Sheehan DV, Lecrubier Y, Sheehan KH, Amorim P, Janavs J, Weiller E, et al. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. J Clin Psychiatry. 1998;59 Suppl 20:22-33;quiz 34-57.

13. Clinical Global Impressions Scale (CGI) [Internet]. Simple and Practical Mental Health. [cited 2020 Nov 27]. Available from: https://simpleandpractical.com/clinical-global-impressions-scale-cgi/

14. Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. British Journal of Psychiatry. 1979;134(4):382–389.

15. Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophrenia Bulletin. 1987;13(2):261–276.

16. Стоянов Д, Кандиларова С, Сираков Н, Стоева М, Велкова К, Stoyanov D, et al. Психиатрията в криза : възможности на транслационното функционално невроизобразяване Psychiatry in crisis : potentialities of translational functional neuroimaging. 2017;2(2):134–141.

17. Bora E, Fornito A, Pantelis C, Yücel M. Gray matter abnormalities in Major Depressive Disorder: a meta-analysis of voxel based morphometry studies. J Affect Disord. 2012 Apr;138(1–2):9–18.

18. Gur RE, Turetsky BI, Cowell PE, Finkelman C, Maany V, Grossman RI, et al. Temporolimbic Volume Reductions in Schizophrenia. Arch Gen Psychiatry. 2000 Aug 1;57(8):769.

19. Gur RE, Cowell PE, Latshaw A, Turetsky BI, Grossman RI, Arnold SE, et al. Reduced Dorsal and Orbital Prefrontal Gray Matter Volumes in Schizophrenia. Arch Gen Psychiatry. 2000 Aug 1;57(8):761.

20. Maggioni E, Crespo-Facorro B, Nenadic I, Benedetti F, Gaser C, Sauer H, et al. Common and distinct structural features of schizophrenia and bipolar disorder: The European Network on Psychosis, Affective disorders and Cognitive Trajectory (ENPACT) study. PLOS ONE. 2017 Nov 14;12(11):e0188000.

21. Shao J, Meng C, Tahmasian M, Brandl F, Yang Q, Luo G, et al. Common and distinct changes of default mode and salience network in schizophrenia and major depression. Brain Imaging and Behavior. 2018 Dec 1;12(6):1708–19.

22. Leech R, Braga R, Sharp DJ. Echoes of the Brain within the Posterior Cingulate Cortex. J Neurosci. 2012 Jan 4;32(1):215–22.

23. Maddock RJ, Garrett AS, Buonocore MH. Remembering familiar people: the posterior cingulate cortex and autobiographical memory retrieval. Neuroscience. 2001 Jun 14;104(3):667–76.

24. Buckner RL, Andrews-hanna EJR, Daniel, Schactera L. The brain's default network: anatomy, function, and relevance to disease. Ann N Y Acad Sci. 2008;1–38.

25. The role of the posterior cingulate cortex in cognition and disease [Internet]. [cited 2020 Nov 25]. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3891440/

26. Nakao T, Radua J, Rubia K, Mataix-Cols D. Gray matter volume abnormalities in ADHD: voxel-based meta-analysis exploring the effects of age and stimulant medication. Am J Psychiatry. 2011 Nov;168(11):1154–63.

27. Newell KA, Zavitsanou K, Huang X-F. Ionotropic glutamate receptor binding in the posterior cingulate cortex in schizophrenia patients. Neuroreport. 2005 Aug 22;16(12):1363–7.

28. Lundstrom B. Isolating the retrieval of imagined pictures during episodic memory: activation of the left precuneus and left prefrontal cortex. NeuroImage. 2003 Dec;20(4):1934–43.

29. Lundstrom BN, Ingvar M, Petersson KM. The role of precuneus and left inferior frontal cortex during source memory episodic retrieval. NeuroImage. 2005 Oct;27(4):824–34.

30. Vogeley K, May M, Ritzl A, Falkai P, Zilles K, Fink GR. Neural correlates of first-person perspective as one constituent of human self-consciousness. J Cogn Neurosci. 2004 Jun;16(5):817–27.

31. Farrow TF, Zheng Y, Wilkinson ID, Spence SA, Deakin JF, Tarrier N, et al. Investigating the functional anatomy of empathy and forgiveness. Neuroreport. 2001 Aug 8;12(11):2433–8.

32. Vatansever D, Manktelow AE, Sahakian BJ, Menon DK, Stamatakis EA. Angular default mode network connectivity across working memory load. Hum Brain Mapp. 2016 Aug 4;38(1):41–52.

33. Seghier ML. The Angular Gyrus. Neuroscientist. 2013 Feb;19(1):43–61.

34. Farrer C, Franck N, Frith CD, Decety J, Georgieff N, d'Amato T, et al. Neural correlates of action attribution in schizophrenia. Psychiatry Research: Neuroimaging. 2004 May 30;131(1):31–44.

35. Niznikiewicz M, Donnino R, McCarley RW, Nestor PG, Iosifescu DV, O'Donnell B, et al. Abnormal Angular Gyrus Asymmetry in Schizophrenia. AJP. 2000 Mar 1;157(3):428–37.

36. Sanches M, Caetano S, Nicoletti M, Monkul ES, Chen HH, Hatch JP, et al. An MRI-based approach for the measurement of the dorsolateral prefrontal cortex in humans. Psychiatry Res. 2009 Aug 30;173(2):150–4.

37. Goldman-Rakic PS. Architecture of the prefrontal cortex and the central executive. Ann N Y Acad Sci. 1995 Dec 15;769:71–83.

38. Greene J, Sommerville R, Nystrom L, Darley J, Cohen JD. An fMRI Investigation of Emotional Engagement in Moral Judgment. Science. 2001;

39. Monsell S. Task switching. Trends Cogn Sci. 2003 Mar;7(3):134–40.

40. Chan RCK, Shum D, Toulopoulou T, Chen EYH. Assessment of executive functions: Review of instruments and identification of critical issues. Arch Clin Neuropsychol. 2008 Mar 1;23(2):201–16.

41. Ito A, Abe N, Fujii T, Hayashi A, Mori E. The contribution of the dorsolateral prefrontal cortex to the preparation for deception and truth-telling. Brain Research. 2012;

42. Yoon JH, Minzenberg MJ, Ursu S, Walters R, Wendelken C, Ragland JD, et al. Association of Dorsolateral Prefrontal Cortex Dysfunction With Disrupted Coordinated Brain Activity in Schizophrenia: Relationship With Impaired Cognition, Behavioral Disorganization, and Global Function. Am J Psychiatry. 2008 Aug;165(8):1006–14.

 doi:10.20944/preprints202012.0031.v1

43. Kandilarova S, Stoyanov D, Kostianev S, Specht K. Altered resting state effective connectivity of anterior insula in depression. Frontiers in Psychiatry. 2018;9(MAR):1–7.

44. Uddin LQ. Salience processing and insular cortical function and dysfunction. Nat Rev Neurosci. 2015;16(1):55–61.

45. Power JD, Cohen AL, Nelson SM, Wig GS, Barnes KA, Church JA, et al. Functional network organization of the human brain. Neuron. 2011 Nov 17;72(4):665–78.