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Is there a relationship between resting state connectivity within large-scale functional networks and implicit motor learning impairments in schizophrenia and bipolar disorder?

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Summary

Aim. The aim of this exploratory study is to evaluate whether implicit motor learning impairments observed in schizophrenia (SZ) and bipolar disorder (BD) are associated with the resting state functional connectivity (rs-FC) within large-scale functional networks.

Method. The study involved 30 BD patients, 30 SZ patients and 30 healthy controls (HC). Implicit motor learning was evaluated with the use of serial reaction time task (SRTT). Prior to the training patients underwent resting state functional magnetic resonance imaging (rsfMRI) examination. We have measured rs-FC within salience network (SAN), default mode network (DMN), frontoparietal network (FPN), sensorimotor network (SMN), limbic network (LN) and visual network (VIN) and their associations with implicit motor learning indices.

Results. rs-FC within SAN, DMN, FPN, SMN, LN and VIN reveal no significant association with implicit motor learning indices. BD, SZ and HC groups did not differ in terms of rs-FC within abovementioned networks.

Conclusions. We have shown that in the studied groups SRTT performance could not be predicted by rs-FC within the major large-scale functional networks, i.e., SMN, FPN, VIN, LN, SAN and DMN. The observation of the independence of implicit motor learning from the initial activity of these systems is important for proper understanding of neuronal underpinnings of this process and planning further neuroimaging research on this topic.

Key words: procedural learning, motor functions, visuomotor learning

Introduction

The concept of "schizophrenia-bipolar disorder boundary" suggests that both clinical groups may share neurodevelopmental and genetic alterations, potentially leading to overlapping neuropsychological and neurological deficits, along with their neurobiological underpinnings [1]. Our studies show that both conditions share motor dysfunctions in the form of neurological and cerebellar soft signs, eye movement disturbances and procedural learning deficits [2–7]. For the first time we have shown that both conditions reveal similar implicit motor learning impairments with the unique pattern of paradoxical, reversed learning curve measured with the use of the Serial Reaction Time Task (SRTT) [5, 8–10]. This method requires participants to press a specific button in response to stimuli shown on a screen, like pressing the button "1" when the digit "1" appears. The subjects are not aware that these stimuli occur in a repetitive pattern. These sequences are interspersed within blocks of randomly ordered stimuli. A consistent reduction in response time (RT) as the same sequences are repeatedly presented, followed by an increase when faced with random sequences (rebound effect), serves as a measure of implicit motor sequence learning [11]. Contrary to healthy individuals, in the group of patients diagnosed with schizophrenia (SZ) and bipolar disorder (BD) repetition of the movement sequence resulted in worse performance reflected in increased reaction times, with the surprising improvement of tapping speed during response to random stimuli. So far, such an atypical pattern of implicit motor learning has been demonstrated only in the group of patients with prefrontal lesions [12].

There is scarce research on neuronal correlates of implicit motor learning impairments in SZ and BD patients. Previous studies implementing functional magnetic resonance imaging (fMRI) to evaluate neuronal underpinnings of those deficits did not replicate the presence of implicit motor learning disturbances in both clinical groups [13–15]. Those results are most likely related with the procedures that have been used [16]. All of the fMRI studies evaluating implicit motor learning in SZ used SRTT variant that consequently does not differentiate patients and HC groups [16]. The only neuroimaging study that measured implicit motor deficits in BD used SRTT with a relatively simple sequence that was recognized by the patients, which most likely made the learning process more explicit [9].

Recently, we have developed a new SRTT variant, specifically adapted to the settings of fMRI experiment [10]. With the use of that procedure, we have repli-

cated our previous findings of implicit motor learning impairments in SZ and BD, including the presence of paradoxical learning curve in those conditions [10]. The next step of our research is to evaluate neuronal underpinnings of those deficits with the use of the novel SRTT variant. For this purpose, we aim to use resting state fMRI (rs-fMRI), a promising non-invasive technique that enables evaluation of the intrinsic architecture of functional brain abnormalities in SZ and BD [17–20]. This method may be used to assess properties of large-scale functional networks, distributed sets of synchronically activated neural structures that correspond with cognitive processes. Those systems include, i.a., salience network (SAN), default mode network (DMN), frontoparietal network (FPN), sensorimotor network (SMN), limbic network (LN) and visual network (VIN). The aim of this exploratory study is to evaluate whether implicit motor learning impairments observed in SZ and BD are associated with the resting state functional connectivity (rs-FC) within these large-scale functional networks.

Methods

Participants

The research involved a subgroup of participants that underwent novel limited response time SRTT variant discussed in our prior work [10], encompassing 30 schizophrenia (SZ) and 30 bipolar disorder (BD) patients, comprising both BD type I (12 participants) and BD type II (18 participants), as well as 30 healthy controls (HC). Diagnoses and clinical assessments were conducted by qualified psychiatrists following the DSM-5 and ICD-10 guidelines. For the BD group, inclusion was based on a euthymic state, defined as scoring less than 11 on the Montgomery–Åsberg Depression Rating Scale [21] and under 5 on the Young Mania Rating Scale [22]. SZ patients were included during symptomatic remission, characterized as scoring three or fewer points on each Positive and Negative Syndrome Scale item. In order to ensure pharmacological homogeneity, both patient groups received antipsychotics belonging to the group of dibenzoxazepines (quetiapine, olanzapine, or clozapine). Lithium treatment was excluded due to its potential effect on motor performance and cerebellar functions [23]. Lamotrigine and valproic acid treatment was allowed. Exclusion criteria included a history of substance use according to DSM-5, unstable chronic/severe/acute somatic diseases, severe personality disorders, and any treatment outside those specified. HC subjects were recruited from the authors' social network and also reviewed by an experienced psychiatrist. This group had no neurological or mental disorder history and met none of the patient exclusion criteria.

The SZ, BD, and HC groups were matched in terms of age and sex, while patient groups were additionally matched for treatment duration. Demographic details of these groups are outlined in Table 1. The Jagiellonian University Bioethical Commit-

tee granted approval for the study. All participants provided written informed consent before being assessed.

Table 1. **Demographic characteristics of the studied groups (extracted from [10])**

Groups	BD	SZ	HC
Age (mean (SD))[a]	38.3 (11.88)	40.57 (12.38)	39.73 (11.63)
Sex (men/women)[b]	18/12	12/18	16/14
Years of education (mean (SD))[a]	16.27 (2.68)	15.3 (2.67)	15.33 (2.12)
Duration of treatment (mean number of years (SD))t[c]	8.2 (6.98)	10.47 (6.75)	-
Equivalent of olanzapine daily dosage (mg/day, (SD))[c]	10.17 (5.3)	11.79 (6.1)	-
BD type (I/II)	13/17	-	-

There were no statistically significant differences between studied groups in terms of abovementioned parameters.

SZ – schizophrenia; BD – bipolar disorder; HC – healthy controls; SD – standard deviation [a] One-way ANOVA; [b] $\chi 2$ test; [c] T-test

Implicit motor learning measurements

Patients performed ambidextrous, limited response time SRTT variant in the MRI setting. Patients were instructed to press the button with the number corresponding to the digit from 1 to 4, displayed on the screen. In the case of the right hand, patients had to press the button number one with the index finger, button number two with the middle finger, button number three with the ring finger, and button number four with the little finger. In the case of the left hand the order was reversed. The task required responses to 500 stimuli, which were divided into five blocks. Blocks from two to four consisted of ten repetitions of 10-digit sequences of numbers from 1-4. Blocks number one and five comprised random digits. The median of reaction time was calculated for each block and divided by the median of reaction time from the first block in order to normalize subjects' performance (mRT%). Two major indices of implicit motor learning were used in this study: (1) rebound, defined as the difference between mRT% in the last block consisting of a sequence and the last one comprising random numbers; (2) difference between mRT% between the first and the last block consisting of the sequence. A thorough description of the procedure and behavioural data analysis has been presented in our recent study [10].

MRI acquisition

The MRI acquisition method was based on our prior study [24]. MRI scans were conducted using a Siemens Skyra MR System (Siemens Medical Solutions, Erlangen, Germany). Structural images were captured using a sagittal 3D T1-weighted MPRAGE sequence. We collected rs-fMRI EPI images over 13 minutes and 20 seconds with gradient-echo single-shot echo planar imaging sequence, utilizing the specs of TR = 800 ms; TE = 27 ms; slice thickness = 0.8 mm, voxel size = 3 mm^3, no gap, and a 60-channel coil. The session yielded 52 interleaved transverse slices across 1,000 volumes. Participants were instructed to keep their eyes open and not to think about anything during the scanning procedure. To improve the sensitivity of the hemodynamic response, simultaneous multi-slice acquisition was used, decreasing the TR to just 0.8 seconds.

Imaging data preprocessing

Preprocessing of the rs-fMRI data was conducted using DataProcessing & Analysis for Brain Imaging (DPABI) V6.0 [25] and Statistical Parametric Mapping software SPM 12 (Wellcome Trust Centre for Neuroimaging, UCL, London, United Kingdom), within the MATLAB R2018a environment (The MathWorks, Inc., Natick, MA, USA). The preprocessing included the following steps: (a) DICOM to Nifti format data conversion; (b) exclusion of the first 10 time points to avoid the effects of magnetic field instability; (c) slice timing correction; (d) realignment – the maximum deviation criterion was <3mm or <3°; (e) voxel specific head motion – analysis and detection of head movements with an accuracy of 1-2 voxels; (f) coregistration Fun-T1 – the data of each subject were checked for matching functional (EPI) to structural data (T1), based on anatomical landmarks; (g) cropping and reorienting T1 images; (h) T1 Segmentation + DARTEL brain segmentation and normalization; (i) T1 coregistration to Fun; (j) normalization using EPI template to the MNI space; (k) covariates regression – removing signal from white matter and cerebrospinal fluid; (l) CompCor – principal component analysis of the first five components.

Functional connectivity analysis

Region of interest (ROI)-to-ROI FC analysis was performed to evaluate the resting state activity within the following large-scale functional networks: SAN, DMN, FPN, SMN, LN, VIN. Selection of ROIs was based on the Harvard-Oxford Atlas, with their localization determined by their x, y, and z-axis coordinates. Each subject's raw time courses were obtained using the "ROI Signal Extractor" module within the Data Processing & Analysis for Brain Imaging (DPABI) V4.3 [26], utilizing MATLAB version R2018a in conjunction with SPM 12.

Functional networks were defined by the following ROIs:

(1) DMN: DefaultMode.MPFC (1,55,-3), DefaultMode.LP (L) (-39,-77,33), DefaultMode.LP (R) (47,-67,29), DefaultMode.PCC (1,-61,38);
(2) SMN: SensoriMotor.Lateral (L) (-55,-12,29), SensoriMotor.Lateral (R) (56,-10,29), SensoriMotor.Superior (0,-31,67);
(3) VIN: Visual.Medial (2,-79,12), Visual.Occipital (0,-93,-4),Visual.Lateral (L) (-37,-79,10), Visual.Lateral (R) (38,-72,13);
(4) SAN: Salience.ACC (0,22,35), Salience.AInsula (L) (-44,13,1), Salience.AInsula (R) (47,14,0), Salience.RPFC (L) (-32,45,27), Salience.RPFC (R) (32,46,27), Salience.SMG (L) (-60,-39,31), Salience.SMG (R) (62,-35,32);
(5) FPN: FrontoParietal.LPFC (L) (-43,33,28), FrontoParietal.PPC (L) (-46,-58,49), FrontoParietal.LPFC (R) (41,38,30), FrontoParietal.PPC (R) (52,-52,45).

Statistical analysis

Demographic variables were evaluated with the use of one-way ANOVA, T-tests, and chi-square tests as applicable. Detailed comparisons have been presented in [10]. One-way ANOVA was utilized to compare rs-FC across ROIs within neural networks such as the SAN, DMN, FPN, SMN, LN, and VIN between SZ, BD and HC groups. These findings were then adjusted using the Benjamini & Hochberg method [26] False Discovery Rate (FDR, $p < 0.05$) and further examined through Bonferroni post-hoc tests. Antipsychotic daily doses were normalized to olanzapine equivalents based on the method by Leucht et al. [27].

Pearson correlations were employed to analyze the relationships between implicit motor learning indices (rebound, and the difference between mRT% between the first and last block consisting of the sequence), rs-FC measures, demographic and clinical data (age, duration of treatment, education level, and olanzapine dose equivalents).

Results

There were no significant differences between SZ, BD and HC groups in terms of rs-FC within SAN, DMN, FPN, SMN, LN, and VIN. The rs-Fc within the abovementioned networks was not correlated with implicit motor learning indices measured with SRTT, participants' age, treatments duration, years of education, or the equivalent of the daily dose of olanzapine.

Discussion

To our best knowledge, this is the first study evaluating the association between rs-FC within the set of large-scale functional networks and implicit motor learning impairments in BD and SZ. We have shown that in the studied groups SRTT performance

could not be predicted by FC within resting state networks related to sensorimotor control (SMN), executive functions (FPN), visual system (VIN), emotion regulation (LN), detection of relevant stimuli (SAN) and internally-oriented cognitive process (DMN). The observation of the independence of implicit motor learning from the pre-training activity within these networks is important for proper understanding of neuronal underpinnings of this process and planning further neuroimaging research on this topic. Interactions between DMN, SAN and FPN are often called canonical as they play a role in almost all cognitive functions [28]. DMN activity is observed during resting (task-negative) state and to a lesser extent during low-effort cognitive processes [29]. Tasks requiring high cognitive involvement are associated with DMN disengagement and activation of FPN, which is related with task selection and executive functions. This system integrates inputs from disparate brain networks to facilitate high-order cognitive functions including working memory and attentional control [28]. SAN plays a role of dynamic switch between resting state and task-related activity mediated by DMN and FPN. Electrophysiological studies suggest that implicit motor learning is associated with disengagement of top-down influences of working memory and attention control related to FPN functions [30–32]. While DMN is usually down-regulated during task performance, low-effort automatic processes such as pressing a button corresponding with the number displayed on the screen may involve activity of this network [29]. Thus, implicit motor learning through SRTT is most likely related to low-level recruitment of both DMN and FPN and does not depend on dynamic switch between those systems provided by SAN. The abovementioned mechanisms may explain why rs-FC within DMN, FPN and SAN cannot predict implicit motor learning performance during SRTT task.

Berns et al. [33] have shown that during SRTT performance, BD patients reveal widespread limbic network activation in response to the new sequence. This reaction has been attributed to arousal and interpreted as a congruent with the symptom of affective lability observed in this condition, indicating that patients' performance in a nonemotional motor task may be altered through the activation of limbic circuitry [33]. However, it should be noted that in the abovementioned study, after each block of the task, participants had two-minute-long rest periods during which they received feedback about their task performance [9, 33]. It has been shown that both positive and negative feedback after SRTT performance significantly affects FC measures across different networks that may overlap with LN [34]. In our study, we have evaluated BD patients in a stable period of euthymia, who do not differ with HC in terms of rs-FC within LN. Thus, patients did not present any behavioural nor neurofunctional indicators of the affective lability before performance of the task. Moreover, BD patients' pre-training resting state activity within LN was not able to predict their implicit motor learning performance. Thus, we suggest that the widespread limbic network activity observed in the study of Berns et al. [33] was more likely related to

the feedback response rather than the preexisting affective lability that disrupts BD patients' motor performance.

In the original version of SRTT, the target stimulus was displayed in one of the four different spatial positions on the screen and participants were required to respond by pressing the spatially congruent response key. In a recent opinion paper, Pedraza et al. [35] emphasized that many studies using this paradigm neglect the presence of strong visuospatial aspects of this task, which are reflected in the fact that subjects need to continuously perceive the visual target in different locations. The authors stated that SRTT is not a motor, but a visuomotor learning task with a significant component of perceptual factors involved in this process [35]. In our studies, we have implemented SRTT variant in which the stimuli were always displayed in a single position in the middle of the screen, in order to minimize the impact of the visuospatial component on patients' performance. Our results have shown that rs-FC within large-scale networks encompassing circuits involved in visuomotor learning, particularly VIS, SMN and FPN cannot predict subjects' performance in SRTT variant with a fixed location of the visual target. This observation may suggest that implicit sequence learning in this procedure may be less dependent on functional changes within brain areas processing perceptual factors. Ideally, these findings should be replicated in a study where rs-FC will be compared between separate groups performing SRTT variants with single and multiple visual target locations, which would allow to evaluate the contribution of visuospatial and motor-related functional networks to the implicit learning indices measured in this task.

Our results present that implicit motor learning impairments in BD and SZ are not related to alterations of the rs-FC within commonly evaluated large-scale functional networks such as DMN, SAN, SMN, FPN, LN and VS. A promising approach to establish rs-FC changes related to implicit motor learning is to define the SRTT-relevant network. A recent study by Baldassarre et al. [36] evaluated associations between pre-training rs-FC and implicit motor learning. Before training, subjects underwent a fMRI session during which they performed SRRT with only random sequences. The set of brain areas that presented peak activity during the test were defined as the task-relevant network. The authors have shown that pre-training rs-FC within this system comprising of cerebellar, cortical and subcortical areas predicted SRTT outcome. It has been demonstrated that individuals with stronger cerebellar pre-training rs-FC exhibited better sequence-specific learning [36]. A growing number of studies presents that the cerebellum is related not only to motor but also cognitive and affective functioning [37–40], and may play a significant role in the pathophysiology of BD and SZ [41]. The aim of our future research is to establish the SRTT-task network in BD and SZ patients during implicit motor learning performance and evaluate its rs-FC properties and associations with behavioural measures.

The limitations of our study involve a relatively small number of subjects and the fact that patients were not drug-naïve, which might influence the outcomes. Nonethe-

less, we demonstrated that the equivalent of the daily doses of olanzapine does not correlate with rs-FC measures. This finding aligns with recent research suggesting that antipsychotic medication does not affect the strength of connectivity in BD and SZ [42]. A thorough discussion of the limitations concerning the SRTT procedure has been presented in our previous studies [5, 10].

Conclusions

In conclusion, we shown that in the studied groups SRTT performance could not be predicted by rs-FC within the major large-scale functional networks, e.g., SMN, FPN, VIN, LN, SAN and DMN. The observation of the independence of implicit motor learning from the initial activity of these networks is important for the proper understanding of neuronal underpinnings of this process and planning further neuroimaging research on this topic.

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