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Disrupted implicit motor sequence learning in schizophrenia and bipolar disorder revealed with ambidextrous Serial Reaction Time Task

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ABSTRACT

Background: Impairment of implicit motor sequence learning was shown in schizophrenia (SZ) and, most recently, in bipolar disorder (BD), and was connected to cerebellar abnormalities. The goal of this study was to compare implicit motor sequence learning in BD and SZ.

Methods: We examined 33 patients with BD, 33 patients with SZ and 31 healthy controls with a use of ambidextrous Serial Reaction Time Task (SRTT), which allows exploring asymmetries in performance depending on the hand used.

Results: BD and SZ patients presented impaired implicit motor sequence learning, although the pattern of their impairments was different. While BD patients showed no signs of implicit motor sequence learning for both hands, the SZ group presented some features of motor learning when performing with the right, but not with the left hand.

Conclusions: To our best knowledge this is the first study comparing implicit motor sequence learning in BD and SZ. We show that both diseases share impairments in this domain, however in the case of SZ this impairment differs dependently on the hand performing SRTT. We propose that implicit motor sequence learning impairments constitute an overlapping symptom in BD and SZ and suggest further neuroimaging studies to verify cerebellar underpinnings as its cause.

1. Introduction

Implicit motor learning relies on improving a sequence of motor acts through their repetition without conscious awareness of the exposure to the task. This type of learning plays a critical role in the structuring of our skills, perceptions and behavior (Dayan and Cohen, 2011; Ferrucci and Priori, 2014; Meltzoff et al., 2009). It can be assessed with the Serial Reaction Time Task (SRTT). In this task, the participant is asked to react to the stimulus on the screen by pressing a button that corresponds to a given stimulus (eg. numeric button 1 to a visually presented digit 1 on the screen, see (Chrobak et al., 2015a) for details). The set of stimuli creates a repetitive sequence, which is unknown to the participant. This sequence is nested in blocks of random order stimuli, which allows to compare a change in reaction time (RT) between blocks with repetitive sequence and blocks with random-order stimuli. The difference between these two is commonly used as an indicator of implicit learning (Chrobak et al., 2014a; Nissen and Bullemer, 1987).

The key structures engaged in implicit motor sequence learning during SRTT are those related to motor functions, i.e. primary motor cortex, premotor area, posterior parietal cortex, prefrontal cortex, striatum and the cerebellum (Dayan and Cohen, 2011; Tzvi et al., 2014). Primary motor cortex, the source of the main motor cortical output, has been shown to participate in sequence learning during early stage of motor consolidation (Muellbacher et al., 2002; Wilkinson et al., 2010) and long-term retention (Galea et al., 2011; Reis et al., 2009). The involvement of the prefrontal cortex in implicit motor learning has

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Table 1
The description of examined groups. All groups were matched for age and gender. The patients were matched for years of antypsychotic treatment.

	Bipolar disorder	Schizophrenia	Healthy control
Age (mean years ± SD)[1]	42 ± 14	38 ± 11	38 ± 11
Sex (women/men)[2]	23/10	16/17	16/15
Years of education (mean years ± SD)[3]	15 ± 3	15 ± 3*	16 ± 2*
Duration of treatment (mean years ± SD)[4]	11 ± 7	10 ± 8	–
Antipsychotic medication (number of patients, mg, mean daily doses ± SD)			
Clozapine	n = 2 250.00 mg ± 70.71	n = 7 307.14 mg ± 101.77	–
Olanzapine	n = 7 10.71 mg ± 1.89	n = 22 14.77 mg ± 4.75	–
Quetiapine	n = 20 360 mg ± 181.08	n = 4 600 mg ± 216.02	–
Normothymic medication (number of patients, mg, mean daily doses ± SD)			
Valproic acid	n = 16 937.50 mg ± 392.64	–	–
Lamotrigine	n = 3 116.67 mg ± 76.37	–	–

[1] $F(2,94) = 1.32$, $p = 0.123$.
[2] $c^2(2, N = 97) = 3.5$, $p = 0.173$.
[3] $F(2,94) = 2.01$, $p = 0.022$.
[4] $t(64) = 0.59$, $p = 0.559$.
* Post-hoc (cor. Bonferroni): HC had significantly longer education time than SZ ($p = 0.017$).

been supported in studies of individuals with brain injuries and in TMS studies (Gómez Beldarrain et al., 1999; Pascual-Leone et al., 1996). Striatum plays a critical role in encoding motor programs. Activity of this structure increases as learning progresses suggesting its role in storage and retention of the learned sequence (Tzvi et al., 2014). Significant role of striatum in implicit motor learning is supported by the deficiency in acquiring new motor sequences in patients with striatal dysfunctions (Doyon et al., 1997; Jackson et al., 1995; Laforce and Doyon, 2001). Recently, the cerebellum also has been considered to be significant neural correlate of performance in this task (Ferrucci et al., 2013), as it is thought to guide cognitive functions involved in sequence processing and ordering events in the time domain (Pascual-Leone et al., 1993). Damage to the cerebellum can lead to impaired implicit learning, which results in the deterioration of performance of the SRTT. Such results are described in patients with cortical degeneration of the cerebellum and in patients with unilateral focal cerebellar lesions (Gómez-Beldarrain et al., 1998; Pascual-Leone et al., 1993).

Implicit learning impairments in schizophrenia (SZ) have been already described in several studies, included in meta-analysis of Siegert et al. (2008). Deficits observed in SRTT has been reported in seven SZ studies (Exner et al., 2006a, 2006b; Green et al., 1997; Kumari et al., 1997; Pedersen et al., 2008; Schwartz et al., 2003), while five studies suggest normal sequence learning in these patients (Foerde et al., 2008; Karatekin et al., 2009; Purdon et al., 2011; Reiss et al., 2006; Zedkova et al., 2006) as summarized in critical review of Remillard (2013). Recently, we have shown for the first time that Bipolar Disorder (BD) patients also present deficits in this type of learning (Chrobak et al., 2015a). With a use of the ambidextrous version of SRTT we have shown that BD patients did not present any indicators of the implicit learning. Moreover, paradoxically their reaction time increased across repetitions of the sequence and it decreased when the sequence changed to random (Chrobak et al., 2015a).

A growing body of evidence suggests that schizophrenia and bipolar disorder exist in a clinical continuum with partially overlapping symptoms, rather than as discrete division into schizophrenic and affective psychosis (Ivleva et al., 2010). It is observed that in both disorders there is an overlap of neuropsychological deficits, such as executive function and memory impairments; and neurobiological substrates (i.e. prefrontal cortex, cerebellum, see Ivleva et al., 2010 for the review). In our previous study concerning implicit motor sequence learning in BD, we hypothesized that BD and SZ may share common dysfunctions in SRTT (Chrobak et al., 2015a), due to aforementioned shared cognitive and neurobiological deficits. The first aim of this study was to evaluate this hypothesis by comparing SZ patients to BD patients group.

Interestingly, recent data indicates that SZ patients reveal unilateral disruptions of left cerebellar regions associated with motor learning. SZ patients present decreased fractional anisotropy of the lobule V in the left cerebellum and decreased volume of the left Crus I/II, regions shown to be associated with implicit motor learning and its impairment in SZ (Kim et al., 2014; Kühn et al., 2012; Tzvi et al., 2014). Studies indicate that unilateral cerebellar deficits cause a worsened execution of SRTT when performing with a hand ipsilateral to the localization of the damage (Gómez-Beldarrain et al., 1998). To our best knowledge, there are no studies evaluating implicit motor learning in SZ independently for the right and the left hand. In this study we used a procedure proposed by Gómez-Beldarrain et al. (1998) where the SRTT is performed with each hand separately. Based on the aforementioned data on the left sided cerebellar disruptions in SZ, we hypothesize that patients will present more impaired implicit motor sequence learning when performing the task with their left hand. Verifying this hypothesis is the second aim of the study.

2. Materials and methods

2.1. Subjects

33 patients with DSM-5 (American Psychiatric Association, 2013; Łojko et al., 2014) diagnosis of BD (15 Bipolar I and 18 Bipolar II patients, 10 patients had history of psychotic features), 33 patients with DSM-5 diagnosis of SZ and 31 healthy controls (HC) were enrolled for this study. 27 patients from the BD group were described in our previous work (Chrobak et al., 2015a). An experienced psychiatrist performed diagnosis and clinical assessment of the patients. Groups were matched for gender and age (see Table 1). All the participants were right-handed, as measured by the Neurological Evaluation Scale (Chrobak et al., 2015b). There was a significant difference between the level of education in HC and SZ patients, however it is noteworthy that previous study showed no effect of the education level on implicit motor learning in schizophrenia (Stevens et al., 2002). Patients' groups were matched for duration of antipsychotic treatment. Inclusion criteria for the SZ and BD patients were: state of symptomatic remission (PANSS