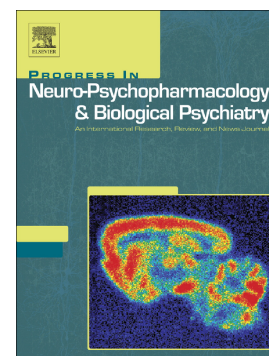# Journal Pre-proof

Relationship between neurological and cerebellar soft signs, and implicit motor learning in schizophrenia and bipolar disorder

Adrian Andrzej Chrobak, Katarzyna Siuda-Krzywicka, Zbigniew Sołtys, Grzegorz Przemysław Siwek, Bartosz Bohaterewicz, Anna Sobczak, Anna Ceglarek, Anna Tereszko, Anna Starowicz-Filip, Magdalena Fąfrowicz, Tadeusz Marek, Marcin Siwek, Dominika Dudek

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Relationship between neurological and cerebellar soft signs, and implicit motor learning in schizophrenia and bipolar disorder.

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Abstract:

Background: Schizophrenia (SZ) and bipolar disorder (BD) patients share deficits in motor functions in the form of neurological (NSS) and cerebellar soft signs (CSS), and implicit motor learning disturbances. Here, we use cluster analysis method to assess (1) the relationship between those abnormalities in SZ and BD and (2) the differences between those groups.

Methods: 33 SZ patients, 33 BD patients as well as 31 healthy controls (HC) took part in the study. We assessed CSS with the International Cooperative Ataxia Rating Scale (ICARS) and NSS with the Neurological Evaluation Scale (NES). Implicit motor learning was evaluated with the Serial Reaction Time Task (SRTT). Participants were divided into clusters (Ward's method) based on the mean response time and mean error rate in SRTT. The difference in ICARS and NES scores, and SRTT variables between clusters were evaluated. We have measured associations between SRTT parameters and both ICARS and NES total scores and subscores.

Results:
Cluster analysis based on the SRTT parameters allowed to extract three clusters. Those were divided according to the increasing disruption of motor functioning (psychomotor retardation, the severity of NSS and CSS) regardless of the diagnosis. Cluster 1 covered almost all of HC and was characterized by faster reaction times and small number of errors. BD and SZ patients represented in cluster 1, although fully functional in performing the SRTT, showed higher rates of NSS and CSS. Patients with BD and SZ were set apart in clusters 2 and 3 in a similar proportion. Cluster 2 presented significantly slower reaction times but with the comparable number of errors to cluster 1. Cluster 3 consisted of participants with normal or decreased reaction time and significantly increased number of errors. None of the clusters were predominantly composed of the patients representing one psychiatric diagnosis.

Conclusions: To our best knowledge, we are presenting the first data indicating the relationship between implicit motor learning and NSS and CSS in SZ and BD patients' groups. Lack of clusters predominantly represented by patients with the diagnosis of SZ or BD may refer to the model of schizophrenia-bipolar disorder boundary, pointing out the similarities between those two disorders.

Keywords: cognitive impairment, motor learning, affective disorders, cerebellum, schizophrenia

1. Introduction:

According to a concept of "schizophrenia-bipolar disorder boundary", schizophrenia (SZ) and bipolar disorder (BD) present a clinical continuum rather than discrete categories of disease (Ivleva et al., 2010). SZ and BD share similarities in symptoms, neurophysiology, neurocognition and neuroanatomy (Ivleva et al., 2010). Recently, there have been a growing interest in the similarities in motor functions disturbances between those disorders (Chrobak et al., 2016, 2014a).

The most extensively studied primary motor impairments in SZ and BD are the Neurological Soft Signs (NSS). NSS constitutes a heterogenic group of symptoms comprising integrative function deficits (expressed in bilateral extinction, agraphesthesia, astereognosis, right/left confusion and impaired audiovisual integration, motor incoordination (exhibited in finger to nose and tandem walk task or manifested in the form of dysdiadochokinesia), impaired sequencing of complex motor acts (pronounced in Ozeretski test, the fist-ring test or the fist-edge-palm test). NSS coexist with cerebellar dysfunction. To account for that, Varambally et al. (2006) introduced the term: cerebellar soft signs (CSS), a set of neurological symptoms specific for cerebellar dysfunctions. CSS are assessed with the International Cooperative Ataxia Rating Scale, assessing posture, kinetic functions, limb ataxia, dysarthria, and oculomotor dysfunctions. Metanalyses consequently point out that NSS differentiate SZ patients from healthy controls (Chan et al., 2010). Studies concerning NSS in BD are much more scarce, however they collaboratively indicate that BD patients present a higher rate of these neurological impairments than healthy controls (Bora et al., 2018). Our previous studies demonstrated similar NSS and CSS severity in BD and SZ patients (Chrobak et al., 2016, 2014a).

Growing number of studies point toward implicit motor deficits in SZ and BD (Chrobak et al., 2017, 2015). Implicit motor learning relies on improving a sequence of motor acts through their repetition without conscious awareness of the exposure to the task. Implicit motor learning can be assessed with the use of the serial reaction time task (SRTT). In this task, the participants are asked to respond to a set of stimuli that, unbeknownst to them, are presented in a repetitive order. The blocks with repetitive sequence are nested within blocks with a random presentation of stimuli. The response time difference between the sequence blocks and the random blocks are widely used as an indicator of implicit learning (Chrobak et al., 2014b; Nissen and Bullemer, 1987). Studies on implicit motor deficits in psychosis focused mostly on SZ patients (Siegert et

al., 2008). In our previous studies, we showed that BD patients present implicit motor learning deficits (Chrobak et al., 2015) and that their abnormalities are similar to those observed in patients with SZ (Chrobak et al., 2017).

NSS, CSS and implicit motor learning involve overlapping brain structures within the prefronto-thalamo-cerebellar networks (Tzvi et al., 2017; Zhao et al., 2014). Both BD and SZ reveal significant disruptions of these brain structures, in particular: the supplementary motor area (Caligiuri et al., 2004; Exner et al., 2006), the striatum (Reiss et al., 2006; Chen et al., 2011; Ong et al., 2012), the primary motor cortex (Levinson et al., 2007; Nelson et al., 2007), the prefrontal cortex (Strakowski et al., 2002, Zhao et al., 2014, Wi{\'n}cr{\'y}nska et al., 2018) and the cerebellum (Chrobak et al., 2014b). Some of those neuroanatomical abnormalities relate to motor dysfunctions. For instance, the volume of gray matter in the left cerebellum in SZ patients negatively correlates with motor sequencing dysfunction signs of the NSS scale (Venkatasubramanian et al., 2008). SZ patients presenting movement sequencing abnormalities are characterized by worsened myelination of the left superior cerebellar peduncle (Hüttlova et al., 2014). In implicit motor learning, the aggravation of left-hand performance in SZ may be associated with more pronounced disruptions of lobule V and Crus I/II in the left cerebellum (Kim et al., 2014; Kühn et al., 2012).

Overall, the co-occurrence of implicit motor learning deficits, and NSS and CSS in SZ and BD suggest that motor deficits may represent one of the overlapping symptoms in SZ and BD and reflecting a common genetic and neurodevelopmental impairment. Yet, the link between implicit motor leaning and other motor dysfunctions in SZ and BD is unclear. Here, we explore the profiles of motor functions, as measured with NSS and CSS, in SZ and BD patients depending on their performance in implicit motor learning task. We hypothesize that impairment in implicit motor learning in SZ and BD will be accompanied by impairment of neurological and cerebellar soft signs. To verify this hypothesis, we used dimension reduction and clustering techniques.

2. Methods:

2.1 Subjects:

33 patients with DSM-5 diagnosis of SZ, 33 patients with DSM-5 diagnosis of BD and 31 healthy controls (HC) were enrolled for the study (Tab. 1). The aforementioned groups were

described in our previous work (Chrobak et al., 2017). All participants were right-handed. Groups were matched for sex and age, and patient groups were matched for the duration of antipsychotic treatment. Inclusion criteria for the SZ and BD patients were state of symptomatic remission (PANSS score of three or less on all of its items) and treatment with antipsychotic drugs from the group of dibenzoxazepine (quetiapine, olanzapine or clozapine). Moreover, BD group inclusion criteria were euthymia, i.e. < 11 points in Montgomery-Asberg Depression Rating Scale –MADRS (McDowell, 2006) and< 5 points in Young Rating Scale for Mania (YMRS) (Young et al., 1979). Due to the selection of atypical antipsychotics from the group of dibenzoxazepines, we provided a relative pharmacological homogeneity across BD and SZ patients. This treatment type was chosen to minimize the effect of the treatment on motor performance. In case of BD patients, additional lamotrigine or valproic acid treatment was accepted. Exclusion criteria for patients were also: a history of alcohol or drug abuse (according to substance use disorder of DSM-5); lithium treatment, severe, acute or chronic somatic and neurological diseases, severe personality disorders or treatment other than mentioned in inclusion criteria. HC were recruited via the authors' social network. In the interview performed by an experienced psychiatrist, they all reported a negative history of mental and neurological disorders, had a negative history of mental diseases in family and did not meet any exclusion criteria for patients. All participants signed an informed written consent prior to the assessment. The University Bioethics Committee approved the study

	Bipolar disorder (n=33)	Schizophrenia (n=33)	Healthy control (n=31)
Age (mean years ± SD)[1]	42 ± 14	38 ± 11	38 ± 11
Sex (women/men)[2]	23/10	16/17	16/15
Duration of treatment (mean years ± SD)[3]	11 ± 7	10 ± 8	-----
Bipolar disorder type (type I/type II)	15/18	-----	-----
No. of bipolar disorder patients with a history of psychotic features	10	-----	-----

1) $F_{(2,94)}=1.32$, p=0.123
2) $\chi^2(2, N = 97) = 3.5$, p=0.173
3) $t(64)=0.59$, p=0.559

Table 1. Characteristics of the participants. All groups were matched for age and gender. The patients were matched for years of treatment.

2.2 Assessment of implicit motor learning.

We evaluated implicit motor learning with the use of SRTT, for details see Chrobak et al., 2017). In this task, a single stimulus (a number from 1 to 4) was presented to the participant. Each digit has a corresponding button on the numeric keypad. The participant kept their hand on the keyboard in such a way that each finger was assigned to a given number (e.g. index finger – button No. 1). Participants were asked to press an appropriate button with the assigned finger as fast as possible after the presentation of a stimulus. The presented numbers were arranged in repetitive 10-element sequences (e.g. 3-2-4-1-3-4-4-2-1-3-2). The sequence was repeated multiple times during the task, which the participant was not aware of. This sequence was nested in blocks of random order stimuli, which are presented before and after the series of blocks composed of a repeating sequence. Implicit motor learning occurs in SRTT when reaction time (RT) decreases through the repetition of the sequence. Two major indices reflect implicit motor learning during this task. The first is the decrease of RT across the first and the last block, containing the sequence. The second one, rebound, is the difference of RT between the last block containing the sequence and the final block comprising numbers in random order. The rebound indicates that the observed decrease in RT across the blocks is dependent on the presence of the sequence.

2.3 SRTT analysis

The RT was calculated as the time between the appearance of a number on the screen and the first button press. For each block of SRTT, we calculated a median RT (mRT). In order to normalize the subjects' baseline performance, we divided the mRT from blocks 2 to 4 by the median RT from block 1 and multiply by 100% (median RT as a percent of the block 1, mRT%). This process allowed us to compare subtle differences in learning dynamic despite the vast discrepancies in RT between the patients and HC groups. As an index of implicit learning, we chose the rebound of mRT% between the last block containing the sequence and the final block comprising numbers in random order (mRT% in block 5 -mRT% in block 4). As the second index of implicit learning, we have used the decrease of RT across the first and the last block with the sequence, thus: mRT% in block 2 - mRT% in block 4.

2.4 Assessment of cerebellar and neurological soft signs

CSS were evaluated using International Cooperative Ataxia Rating Scale (ICARS) (Storey et al., 2004; Trouillas et al., 1997). This scale comprises 19 items, divided into 4 subscales:

1. Gait and posture subscore (ICARS-GP), evaluating walking capacities, gait speed, standing capacities, the spread of feet in natural position; body swaying with feet together (with eyes open and separately with eyes closed) and quality of sitting position (34 points).

2. Kinetic functions subscore (ICARS-K), assessing knee-tibia test, finger-nose test (both tremor and decomposition of the movement), finger-finger test, pronation–supination and Archimedes spiral drawing. Knee–tibia test, finger–nose test and pronation–supination test was assessed separately for the left and right limb (52 points).

3. Dysarthria subscores (ICARS-D), assessing fluency and clarity of speech (8 points).

4. Oculomotor subscore (ICARS-O) encompassing gaze-evoked nystagmus, ocular pursuit abnormalities, and dysmetria of the saccade (6 points). Each item shows the subjects' performance in specific task and is rated based on the standardized instructions. Scores vary from 0 to 8 or

0 to 1 in some of the subscales, where 0 represents normal performance and maximum score represents severely affected the performance of specific task. ICARS has been validated in populations of patients with multiple system atrophy, spinocerebellar atrophy 1, 2, 3, 6, 7 and 14, as well as in Friedreich ataxia (Saute et al., 2012).

NSS were evaluated with the use of NES. This scale is comprised of 26 items, grouped into four subscales: Sequencing of complex motor acts (NES-S), Sensory integration (NES-SI), Motor coordination (NES-MC) and Other. Total score, as well as subscores, were rated based on its standardized guidelines (Buchanan and Heinrichs, 1989). All of the abovementioned instruments' scores were collected for statistical analysis.

2.5 Statistical analysis

All statistical analyses were performed with R software (R Core Team 2019). Cluster analysis was performed with normalized main values of SRTT. We have decided to divide

patients into clusters based on SRTT parameters instead of NES and ICARS scores, due to the fact that the first ones represent objective measures (mean reaction times and mean numbers of errors) while the latter ones are result of subjective evaluation made with the use of clinical scales. We believe this approach results in more objective clusterisation of participants. Euclidean distance and Ward's method were selected for establish hierarchical dendrogram, and NbClust package was used to determine the optimal number of clusters. The difference in ICARS, NES scores, SRTT variables and demographical characteristics between clusters were evaluated with the use of Chi-square tests or one-way ANOVA followed by Games-Howell post-hoc test. Pearson's r correlation coefficients were used to evaluate associations between SRTT parameters (mRT, mRT%, sum of errors during SRTT, and indices of implicit motor learning: rebound, difference in mRT% between block 2 and 4) and ICARS, and NES total scores and subscores. Correlations were calculated in groups specified on the basis of diagnosis (BD, SZ, and HC) and within the group revealed through cluster analysis. Pearson's r correlation coefficients were used to evaluate associations between olanzapine equivalent and ICARS, NES and SRTT scores.

3. Results and statistical analyses

Clusterization algorithms revealed a large range of possible cluster numbers, ranging from 2 to 15 clusters. The most frequent values were 3 and 4. We decided to cut-off 3 clusters because such option guaranteed appropriate numbers of cases in each cluster for further analyses (Fig S1).

Cluster 1 consisted of the majority of healthy controls (28 individuals), 11 BD and 13 SZ patients. In further analyses cluster 1 has been divided into groups of HC (cluster 1HC) and the patients' group (cluster 1P). The division was performed to exclude the possibility that any differences between the clusters would be due to the presence of the overwhelming number of HC in cluster 1. Cluster 2 comprised of 3 HC, 17 BD and 10 SZ patients. Cluster 3 consisted of 5 BD and 7 SZ patients. There were no significant differences between Clusters 1P, 2 and 3 in case of gender, age, duration of treatment and medication (mean equivalent of olanzapine). Results of ANOVA tests are summarized in Tab. 2. There were no significant differences between clusters in case of the number of individuals from SZ and BD groups ($\chi2 = 3.0741$, df = 2, p = 0.215). Clusters composition is presented in Fig. 1. We compared the above clusters in terms of implicit

motor learning indices (see Methods), ICARS and NES subscores. All the statistics are summarized in Table 3.

Parameter	F(df)	p
Age	$F_{(2,66)} = 2.75$	0.071
Education	$F_{(2,66)} = 0.27$	0.763
Years of Therapy	$F_{(2,66)} = 0.48$	0.621
Mean equivalent of olanzapine	$F_{(2,66)} = 2.5$	0.090

Table 2. Differences between Clusters 1P, 2 and 3 in case of age and duration of treatment. ANOVA with Welch correction for nonhomogeneous variances.
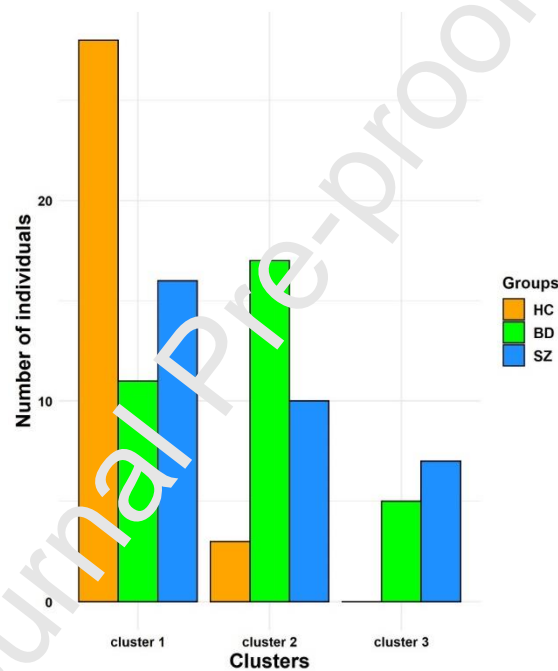

Fig. 1. Clusters composition. There were no significant differences between clusters in case of the number of individuals from SZ, BD and HC groups ($\chi2 = 3.0741$, df = 2, p-value = 0.215). SZ – schizophrenia, BD – bipolar disorder, HC – healthy controls.

3.1 Implicit motor learning indices

Cluster 2 presented significantly higher response times in SRTT (mean mRT) than Clusters 1HC (t(50.01) = 11.55, p<0.001) and 1P (t(54.66) = 8.75, p<0.001). There were no significant differences in mean mRT between Cluster 2 and 3, and between 1HC and 1P (Fig. 2).
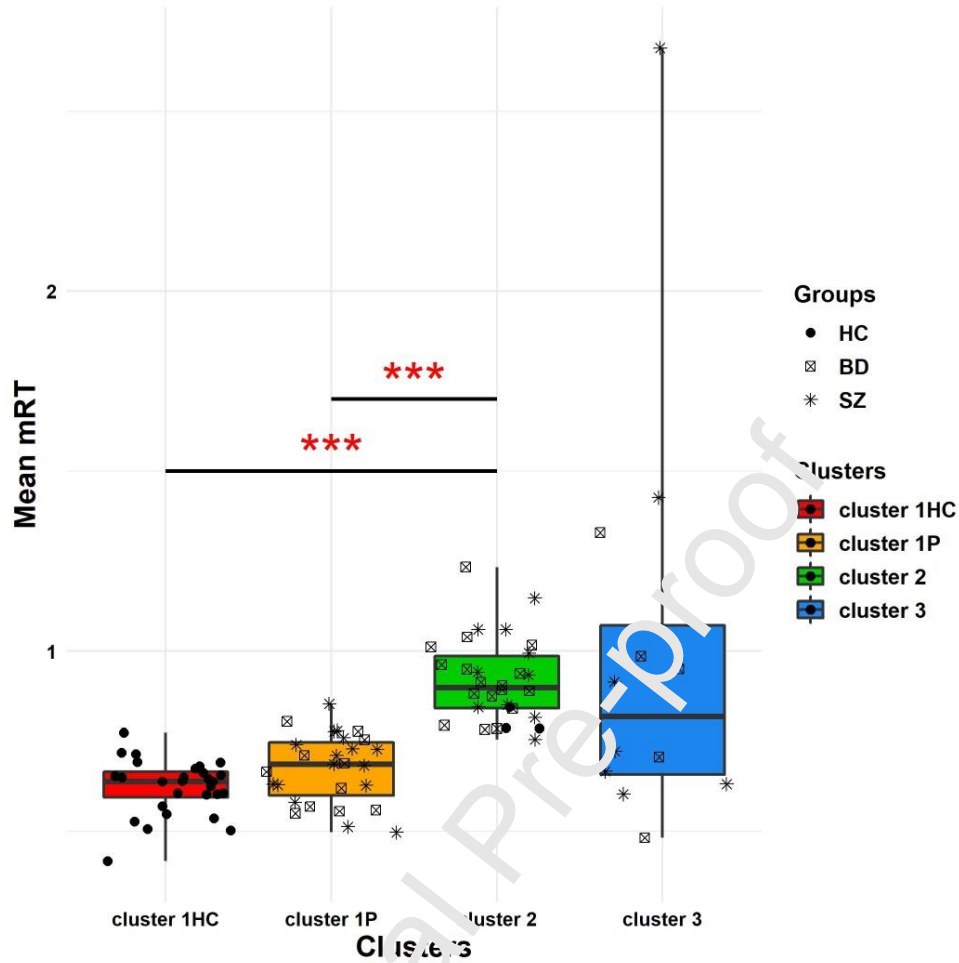
Fig. 2. Differences in mean mRT between the clusters. ANOVA with Welch correction for nonhomogeneous variances has been used (F(3, 35.65) = 45.16, p<0.001). The asterisk denotes statistical significance of Games-Howell post hoc tests. mRT – median reaction time, SZ – schizophrenia, BD – bipolar disorder, HC – healthy controls. *** p < 0.001

In terms of SRTT error rate (mean sum of errors), cluster 3 presented the highest error rate

(significantly different from each of the remaining clusters: 1HC, $t(11.44)=7.22$, $p<0.001$; 1P, $t(11.86)=6.31$, $p<0.001$, and cluster 2, $t(11.52) =7.19$, $p<0.001$); cluster 1HC and 2 did not differ significantly; and cluster 1P showed higher mean number of errors in comparison to cluster 1HC $(t(47.37) = 3.56$, $p=0.005)$. Moreover, there is significant difference between clusters 2 and 1P $(t(50.40) = 3.40$, $p = 0.007)$. Differences in mean number of errors between the clusters are presented in Fig. 3. Associations between mean number of errors and mean mRT are presented in Fig. 4. Cluster 1HC presented significantly higher rebound than clusters 1P $(t(51.26) = 3.03$, $p = 0.02)$ and 2 $(t(50.75)=3.83$, $p = 0.002$, Fig 5).

Fig. 3. Differences in mean number of errors between the clusters. ANOVA with Welch correction for nonhomogeneous variances has been used (F(3, 35.75) = 20.81, p<0.001). The asterisk denotes statistical significance of Games-Howell post hoc tests. SZ – schizophrenia, BD – bipolar disorder, HC – healthy controls. *** p < 0.001

Fig. 4. Associations between mean number of errors and mean median reaction time (mRT) SZ – schizophrenia, BD – bipolar disorder, HC – healthy controls. Ellipses show 95% confidence interval for each cluster
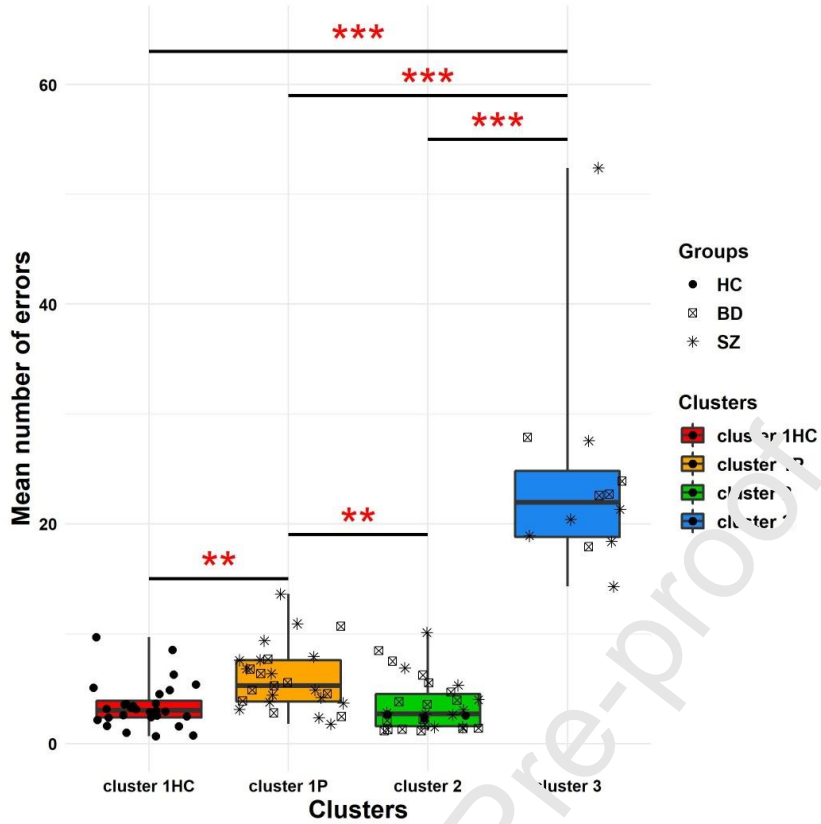
Fig. 5. Differences in mean rebound between the clusters. ANOVA with Welch correction for nonhomogeneous variances has been used (F(3, 93) = 5.83, p=0.001). The asterisk denotes statistical significance of Games-Howell post hoc tests. SZ – schizophrenia, BD – bipolar disorder, HC – healthy controls. ** p < 0.001
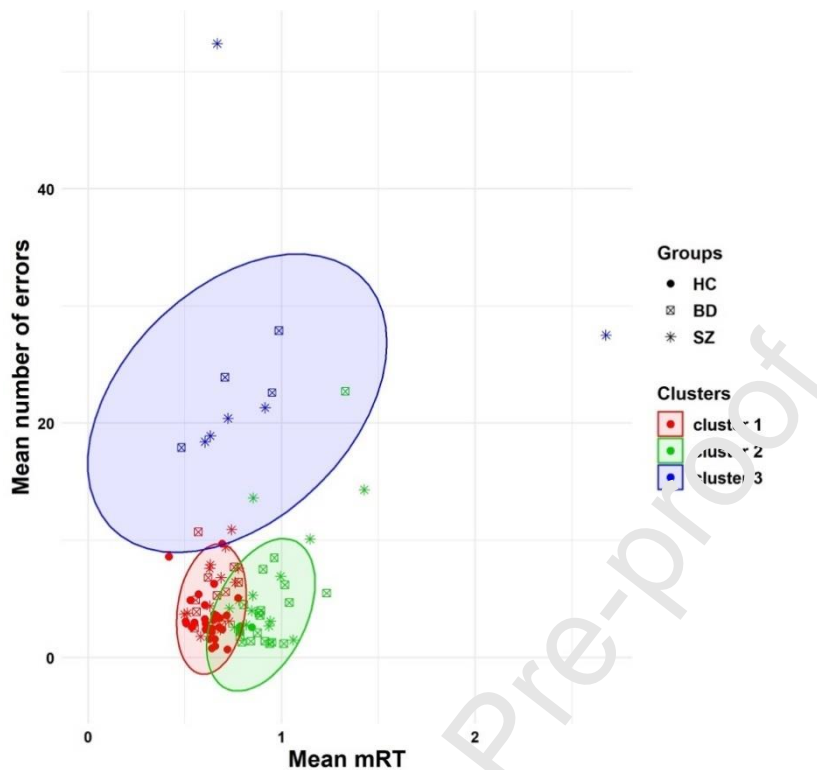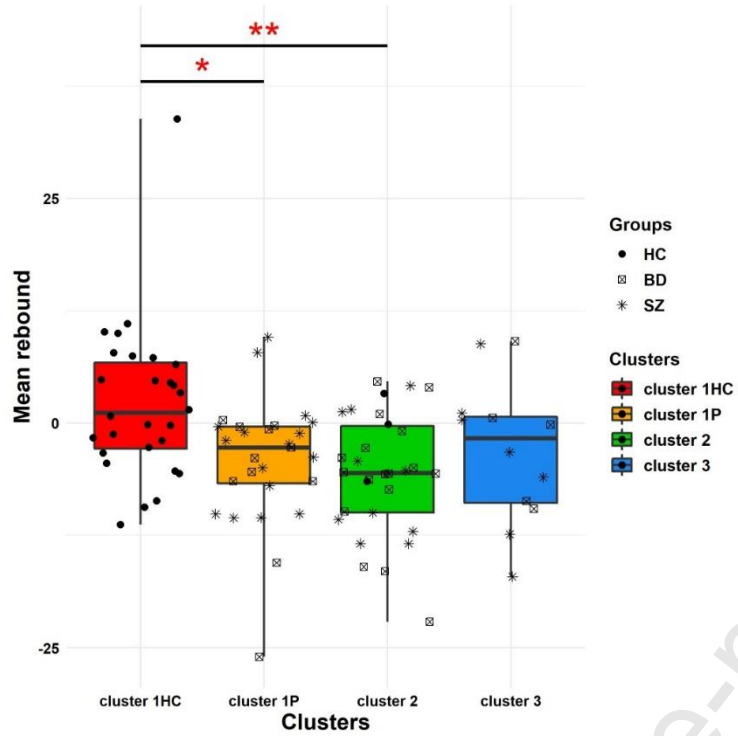
3.2 ICARS

Cluster 1HC showed a significant lower number of points in ICARS total score, gait, and posture, and kinetic functions subscales than clusters 1P, 2, and 3, which did not differ significantly from each other (see Tab. 2). Cluster 1 HC showed significantly lower ICARS dysarthria subscale scores than cluster 3. There were no significant differences between other clusters in terms of this subscale.

3.3 NES

Compared to patients' clusters, cluster 1HC revealed a significantly lower scores in NES motor coordination and sequencing of complex motor acts subscores, as well as the NES total score. There were no significant differences in the abovementioned scores between patient clusters. In terms of NES sensory integration subscores, cluster 1HC showed a significantly lower number of points than cluster 1P and 2. There were no differences in this scale between cluster 1HC and cluster 3, and between clusters 1P, 2 and 3.

Parameter	ANOVA	1HC vs 1P	1HC vs 2	1HC vs 3
ICARS-T*	$F(3, 33.76)=19.66$, $p < 0.001$	$t(34.05) = 5.27$, $p = 0.001$	$t(34.11) = 5.34$, $p < 0.001$	$t(11.61) = 3.74$, $p = 0.014$
ICARS-GP	$F(3, 93)=4.64$ $p < 0.005$	$t(47.16) = 3.03$ $p = 0.02$	$t(52.99) = 3.26$, $p < 0.01$	ns
ICARS-KF*	$F(3, 31.62)=16.28$, $p <= 0.001$	$t(28.11) = 4.54$, $p = 0.001$	$t(29.88) = 4.66$, $p < 0.001$	$t(11.27) = 3.25$ $p = 0.033$
ICARS-D*	$F(3, 30.62)=5.27$, $p = 0.004$	ns	ns	$t(11.10) = 3.09$ $p = 0.044$
ICARS-O*	$F(3, 35.12)=6.79$, $p < 0.001$	$t(35.41) = 7$, $p < 0.001$	$t(39.46) = 2.93$, $p < 0.028$	ns
NES-T*	$F(3, 35.94)=23.32$, $p < 0.001$	$t(45.92) = 4.46$, $p = 0.001$	$t(41.80) = 5.75$, $p < 0.001$	$t(12.15) = 3.63$, $p = 0.016$
NES-SI*	$F(3, 37.41)=9.44$, $p < 0.001$	$t(51.80) = 4.79$, $p = 0.001$	$t(51.28) = 3.91$, $p < 0.002$	ns
NES-C*	$F(3, 31.84)=27.43$, $p < 0.001$	$t(28.01) = 6.32$, $p < 0.001$	$t(31.72) = 5.92$, $p < 0.001$	$t(11.21) = 3.93$, $p = 0.01$
NES-S*	$F(3, 35.23)=19.18$, $p < 0.001$	$t(39.62) = 5.58$, $p < 0.001$	$t(40.48) = 5.68$, $p < 0.001$	$t(11.91) = 3.39$, $p = 0.024$

Table 3. ICARS and NES scores rates across clusters, results of ANOVA and post-hoc Games-Howell test. Significant differences were found only between 1HC and other groups. ICARS – International Cooperative Ataxia Rating Scale; ICARS-T – ICARS total score; ICARS-GP – ICARS gait and posture subscale; ICARS-D – ICARS dysarthria subscale; ICARS-K – ICARS

kinetic subscale; ICARS-O – ICARS oculomotor subscale; NES – Neurological Evaluation Scale, NES-T – NES total score; NES-MC – NES motor coordination subscale; NES-S – NES sequencing of complex motor acts subscale; NES-SI – NES sensory integration subscale. * ANOVA with Welch correction for nonhomogeneous variances.

Differences in rates of NSS and CSS across clusters are presented in Fig 6 and Tab. 3.
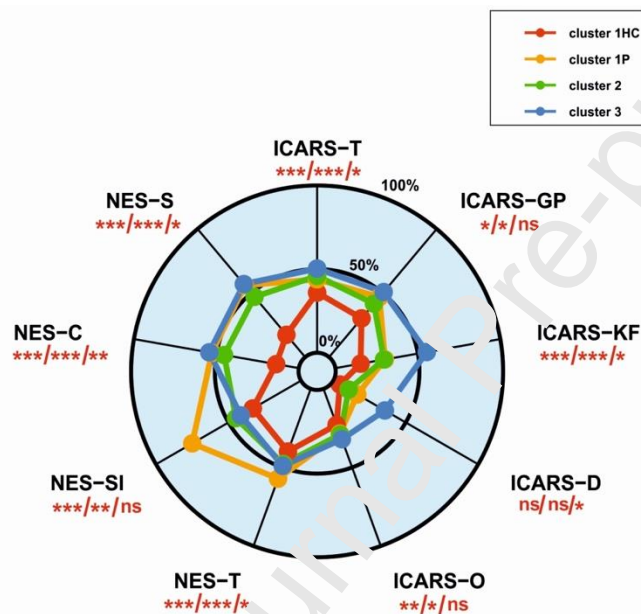
Fig 6. ICARS and NES scores rates across clusters. ICARS – International Cooperative Ataxia Rating Scale; ICARS-T – ICARS total score; ICARS-GP – ICARS gait and posture subscale; ICARS-D – ICARS dysarthria subscale; ICARS-K – ICARS kinetic subscale; ICARS-O – ICARS oculomotor subscale; NES – Neurological Evaluation Scale, NES-T – NES total score; NES-MC – NES motor coordination subscale; NES-S – NES sequencing of complex motor acts subscale; NES-SI – NES sensory integration subscale. The asterisk denotes statistical significance compared to the healthy controls group. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

3.4 Associations between SRTT, NES and ICARS

Table 4 summarizes the associations between implicit motor learning parameters of SRTT and CSS and NSS within the clusters. In summary, in the healthy controls (cluster 1HC) SRTT error rate positively correlated with ICARS total score and ICARS gait and posture subscales, and negatively correlated with ICARS dysarthria and kinetic functions subscales. There was also a negative correlation between ICARS dysarthria and kinetic functions subscales and SRTT reaction times. We also found negative correlations between the NES motor coordination subscore and SRTT reaction times; and positive correlations between the NES sequencing of complex motor acts subscore and the reaction times in block 2 of SRTT (mRT2).

In cluster 1P, ICARS oculomotor subscore was positively correlated with the mean RT rebound between blocks 4 and 5, an index of implicit motor learning. It was also positively correlated with SRTT reaction times in blocks 2, 3 and 5 normalized by the reaction time of block 1 (mRT2%, mRT3% and mRT5%). NES sensory integration subscore correlated positively with reaction times in block 4.

In cluster 2, ICARS kinetic functions subscore positively correlated with SRTT error rate, SRTT reaction times in block 2 (mRT2 and mRT2%), and with the difference in mRT% between blocks 2 and 4. ICARS dysarthria subscore was positively correlated with mRT2 and mRT3. NES total score was positively correlated with mRT2 and mRT2%. NES motor coordination subscore was positively correlated with mean mRT and mRT of blocks 1-4.

In cluster 3 ICARS total score correlated negatively with difference in mRT% between blocks 2 and 4. ICARS gait and posture subscale score was positively correlated with mRT4 and mRT5. ICARS kinetic functions were negatively correlated with the mean rebound.

cluster 1HC									
errors	0.61 ***	0.44*	0.48 **	0.78 ***	-	-	-	-	-
mean mRT	-	-	-0.52 **	-	-	-	-0.43 *	-	-
mRT1 RH	-	-	-0.46 *	-	-	-	-0.39 *	-	-
mRT1 LH	-	-	-0.45 *	-0.39 *	-	-	-0.45 *	-	-
mRT2 RH	-	-	-0.46 *	-	-	-	-	0.41 *	-
mRT2 LH	-	-	-0.47 *	-0.44 *	-	-	-0.43 *	-	-
mRT3 RH	-	-	-0.4 *	-	-	-	-	-	-
mRT3 LH	-	-	-0.47 *	-0.4 *	-	-	-	-	-
mRT4 RH	-	-	-0.45 *	-	-	-	-	-	-
mRT4 LH	-	-	-0.43 *	-0.42 *	-	-	-	-	-
mRT5 RH	-	-	-0.045 *	-	-	-	-0.49 *:	-	-
mRT5 LH	-	-	-0.52 **	-0.42 *	-	-	.45 *	-	-
cluster 1P									
mRT2% RH	-	-	-	-	0.47 *	-	-	-	-
mRT3% RH	-	-	-	-	0.5 **	-	-	-	-
mRT5% RH	-	-	-	-	0.62 ***	-	-	-	-
mRT4 RH	-	-	-	-	-	-	-	-	0.38 *
mean rebound	-	-	-	-	0.3. *	-	-	-	-
cluster 2									
errors	-	-	-	0.4 *	-	-	-	-	-
mean mRT	-	-	-	-	-	-	0.39 *	-	-
mRT1 RH	-	-	-	-	-	-	0.39 *	-	-
mRT2 RH	0.43 *	-	-	.43 *	-	0.41 *	0.52 **	-	-
mRT2 LH	-	-	0.44 *	-	-	-	-	-	-
mRT2% RH	0.37 *	-	-	0.41 *	-	0.37 *	-	-	-
mRT3 RH	-	-	-	-	-	-	0.43 *	-	-
mRT3 LH	-	-	0.4. *	-	-	-	-	-	-
mRT% 2-4	0.39 *	-	-	0.38 *	-	-	-	-	-
cluster 3									
mRT4 RH	-	0.7 *	-	-	-	-	-	-	-
mRT5 RH	-	0.65 *	-	-	-	-	-	-	-
mean rebound	-	-	-	-0.6 *	-	-	-	-	--
mRT% 2-4	-0.59 *	-0.67 *	-	-	-	-	-	-	-

Table 4. Correlations between indices of implicit motor learning in SRTT, mRT, mRT%, error rates and cerebellar and neurological soft signs within clusters. ICARS – International Co-operative Ataxia Rating Scale; ICARS-T – ICARS total score; ICARS-GP – ICARS gait and posture subscale; ICARS-D – ICARS dysarthria subscale; ICARS-K – ICARS kinetic subscale; ICARS-O – ICARS oculomotor subscale; NES – Neurological Evaluation Scale, NES-T – NES total score; NES-MC – NES motor coordination subscale; NES-S – NES sequencing of complex motor acts

subsc   mean

difference in mRT% between blocks 2 and 4; * p < 0.05, ** p < 0.01, *** p < 0.00

Associations between implicit motor learning parameters of SRTT and cerebellar and neurological soft signs within SZ, BD and HC groups are presented in table 5. In the group of BD patients, we have shown that ICARS and NES scores and subscores are associated with slower reaction times (mRT1-5) during implicit motor learning task. NES disrupted sequencing of motor acts and sensory integration subscores were linked with lower improvement of reaction speed during the task (mRT3% and mRT4%). NES sequencing of complex motor acts and ICARS dysarthria subscores were related to lower difference between mRT% of block 2 and 4. In the group of SZ patients, ICARS oculomotor impairments and motor coordination subscores were associated with disrupted improvement of reaction speed (mRT%). NES motor coordination subscores were associated with the increased number of errors during SRTT. We have shown that NES sensory integration and sequencing of complex motor acts subscores were associated with lower implicit motor index (difference between mRT% of blocks 2 and 4) in this clinical group. Finally, we have shown associations between NES and ICARS scores and implicit motor learning parameters in the HC group

	ICARS-T	ICARS-GP	ICARS-D	ICARS-K	ICARS-O	NES-T	NES-MC	NES-S	NES-SI
BD									
errors	-	-	-	-	-	-	-	-	-
mean mRT	0.48 **	0.49 **	-	0.35 *	-	0.42 *	0.38 *	0.41 *	-
mRT1 RH	0.37 *	0.49 **	0.36 *	-	-	-	-	-	-
mRT1 LH	0.37 *	0.46 *	0.37 *	-	-	-	-	-	-
mRT2 RH	0.49 **	0.45 **	-	0.41 *	-	0.45 **	0.45 **	0.36 *	-
mRT2 LH	0.38 *	-	0.46 **	-	-	-	-	-	-
mRT3 RH	0.45 **	0.47 **	-	-	-	0.44 *	0.43 *	0.38 *	-
mRT3% RH	-	-	-	-	-	-	-	-	0.35 *
mRT3 LH	0.38 *	0.38 *	0.5 **	-	-	-	-	-	-
mRT4 RH	0.48 **	0.47 **	0.48 **	-	-	0.47 **	0.43 *	0.5 **	-
mRT4 LH	0.5 **	0.48 **	0.52 **	0.42 *	-	0.39 *	-	0.41 *	-
mRT5 RH	0.48 **	0.48 **	0.49 **	-	-	0.45 **	0.43 *	0.49 **	-
mRT5 LH	0.43 *	0.43 *	0.39 *	0.37 *	-	0.36 *	-	0.35 *	-
SZ									
errors	-	-	0.45 **	-	-	-	0.36 *	-	-
mRT2% RH	-	-	-	-	0.42 *	-	-	-	-
mRT3% RH	-	-	-	-	0.39 *	-	-0.35 *	-	-
mRT5% RH	-	-	-	-	0.44 **	-	-	-	-
mRT% 2-4	-	-	-	-	-	0.37 *	-	0.35 *	0.47 **
HC									
errors	0.61 ***	0.42 *	0.48 **	0.79 ***	-	-	-	-	-
mean mRT	-	-	-0.45 *	-0.37 *	-	-	-0.41 *	0.41 *	-
mRT1 RH	-	-	-0.4 *	-	-	-	-0.4 *	0.38 *	-
mRT1 LH	-	-	-0.36 *	-0.38 *	-	-	-0.4 *	0.37 *	-
mRT2 RH	-	-	-0.45 *	-	-	-	-0.36 *	0.5 **	-
mRT2 LH	-	-	-0.37 *	-0.4 *	-	-	-0.37 *	-	-
mRT3 RH	-	-	-0.39 *	-	-	-	-	0.45 *	-
mRT3 LH	-	-	-0.38 *	-	-	-	-	-	-
mRT4 RH	-	-	-0.41 *	-	-	-	-	0.39 *	-
mRT4 LH	-	-	-0.37 *	-	-	-	-	-	-
mRT5 RH	-	-	-0.41 *	-	-	-	-0.46 **	-	-
mRT5 LH	-	-	-0.42 *	-0.4 *	-	-	-0.4 *	-	-
mRT% 2-4	-	-	-0.38 *	-	-	-	-	-0.44 **	-

Table 5. Correlations between indices of implicit motor learning in SRTT, mRT, mRT%, error rates and cerebellar and neurological soft signs within SZ, BD and HC groups. ICARS – International Co-operative Ataxia Rating Scale; ICARS-T – ICARS total score; ICARS-GP – ICARS gait and posture subscale; ICARS-D – ICARS dysarthria subscale; ICARS-K – ICARS kinetic subscale; ICARS-O – ICARS oculomotor subscale; NES –

motor acts subscale; NES-SI – NES sensory integration subscale.; errors: mean number of errors during SRTT; RH: right hand; LH: left hand; mRT% 2-4: mean difference in mRT% between blocks 2 and 4; SZ: schizophrenia; BD: bipolar disorder; HC: healthy control; * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

4. Discussion

The present study explores the relationship between impaired implicit motor learning and other motor dysfunctions such as NSS, CSS in patients with SZ and BD. Patients and healthy control participants were divided into three clusters based on their implicit motor learning assessed with Serial Reaction Time Task. These clusters corresponded to increased disruption of motor functioning (psychomotor retardation, the severity of NSS and CSS) regardless of the diagnosis. Cluster 1 comprised majority of healthy controls and was characterized by faster reaction times and small number of errors. BD and SZ patients represented in cluster 1, although fully functional in performing the SRTT, showed abnormal motor functioning as measured NSS and CSS. Patients with BD and SZ were set apart in clusters 2 and 3 in a similar proportion. Cluster 2 presented significantly slower reaction times but with the comparable number of errors to cluster 1. Cluster 3 consisted of participants with normal or decreased reaction time and significantly increased number of errors. None of the clusters was predominantly composed of the patients representing one psychiatric diagnosis. Lack of clusters predominantly represented by patients with the diagnosis of SZ or BD may refer to the model of schizophrenia-bipolar disorder boundary, pointing out the similarities between those two disorders.

Our data points out toward associations between SRTT parameters and ICARS and NES scores. In the group of BD patients, we have shown that higher rates of NSS and CSS are associated with slower reaction times (mRT1-5) during implicit motor learning task. Disrupted sequencing of motor acts and sensory integration, measured by NES, were linked with lower improvement of reaction speed during the task (mRT3% and mRT4%). Noteworthy, disturbances of sequencing of complex motor acts and dysarthria scores were related to lower implicit motor learning index (difference between mRT% of block 2 and 4). In the group of SZ patients, oculomotor impairments measured by ICARS and motor coordination disturbances measured by NES were associated with disrupted improvement of reaction speed (mRT%). Higher scores of motor coordination deficits were associated with the increased number of errors during implicit motor learning task. Importantly, we have shown that deficits of sensory integration and sequencing of complex motor acts were associated with lower implicit motor index (difference between mRT% of blocks 2 and 4) in this clinical group. Finally, we have

shown that numerous relationships between NSS and CSS, and implicit motor learning parameters are noticeable in the HC group. Our results corroborates with the results indicating that NSS, CSS and implicit motor learning involve overlapping brain structures within the prefronto-thalamo-cerebellar networks (Tzvi et al., 2017; Zhao et al., 2014).

Our observation that normalized implicit learning index had a positive correlation with sensory integration, sequencing of complex motor acts subscales and total score of NES in SZ patients may indicate relationship between NSS and performance of motor coordination tasks. The above relationship was suggested in literature before. Specifically, Flashman and colleagues revealed that patients with NSS showed poorer performance in finger tapping and other motor coordination tasks in comparison to patients without NSS (Flashman et al., 1996). Our results relate to the aforementioned observation pointing out that NES and ICARS scores may correspond to objectively measured parameters of SRTT. Future studies should furtherly explore associations between CSS and NSS and implicit motor learning with the use of different paradigms, e.g. pursuit rotation task which is not relying on finger tapping. Moreover, NSS are correlated with extrapyramidal side effects like akathisia and tremor, which could affect the performance of the motor tasks (Jahn et al., 2006).

Our study showed that the clustering algorithm, based on the data from performance of the implicit learning task, allows to distribute SZ and BD patients in three different clusters. What is interesting, patients were not divided in regard to the diagnosis, as both SZ and BD were placed in all of the three clusters. Healthy controls, on the other hand, were located mainly in Cluster 1 (90%), with only a few of them in Cluster 2. The last result may be due to the fact that both NSS and CSS are also present in the population of healthy participants (Dazzan et al., 2006; Thomann et al., 2015).

According to our hypotheses, healthy participants, compared to clusters consisting of patients, were characterized by higher rebound as well as lower number of ICARS and NES scores, which indicates that NSS were significantly less represented among healthy participants. As we expected, healthy participants, aggregated in cluster 1HC, had lower mean mRT and lower mean sum of errors compared to other clusters, which indicates better performance in implicit motor learning task. These results are consistent with the literature on altered

performance in reaction time tasks observed in patients compared to healthy subjects (Chrobak et al., 2017) as well as the higher number of NSS in clinical group (Chrobak et al., 2016; Zhao et al., 2014).

Both patients' groups were under the effect of antipsychotic treatment with quetiapine, clozapine or olanzapine. In addition, the BD group was treated with mood stabilizers and valproic acid. There is limited data on the effect of medication (atypical antipsychotics and mood stabilizers) on the SRTT. In our previous work (Chrobak et al., 2015) we have shown that atypical neuroleptics could not affect implicit motor learning in SRTT. In the current study, our results showed that similar intra-cluster variance of task performance is present in both patients with SZ and BD, which might be an additional proof of such lack of dependence.

NSS and CSS, as well as implicit motor learning disruptions, are highly related to impairments displayed by the cerebellum and its connections with cortical and subcortical regions. It stays in line with studies revealing cerebellar abnormalities among patients experiencing NSS (Bottmer et al., 2005; Kong et al., 2020; Shinn et al., 2017). Our results are also coherent with the work of Tzvi et al. (2017), showing the relationship between cerebellar dysfunction and difficulties in motor learning. Future neuroimaging studies are required to identify overlap between structural and functional neuronal underpinnings of NSS, CSS and implicit motor learning dysfunctions.

We are aware of several limitations of this study, such as small subject sample - due to the relatively low number of participants and high variance of measured variables in cluster 3, larger subject sample could potentially lead to better characterization of this group by revealing more differences across clusters. Another limitation is a fact that clinical groups were under the influence of antipsychotic medication, and we did not measure potential antipsychotic induced movement disorders in these groups. A detailed discussion of potential limitation factors was presented in our previous studies (Chrobak et al., 2017, 2016, 2015).

Despite limitations mentioned above, we present the first data indicating the relationship between implicit motor learning and NSS and CSS in SZ and BD patients' group. Hirjak et al., (2016) points out that motor abnormalities are frequently found in mental disorders and they may reflect common neuronal underpinnings e.g. dysfunction of cortico-cerebellar-thalamo-cortical

circuits. Authors proposed application of dimensional approach in studies of motor abnormalities across clinical diagnoses. Cluster analysis carried out on the basis of the implicit motor learning parameters revealed the presence of three main clusters divided according to the increasing motor dysfunctions, regardless of the diagnosis. Thus, our results support the use of transnosological "motor dimension". Stratification of SZ and BD according to the severity of their motor abnormalities may help to: a) characterize structural and functional changes in cortico-cerebellar-thalamo-cortical network across the "motor dimension"; b) evaluate factors associated with motor dysfunctions c) evaluate whether assessment of motor functions may serve as transdiagnostic prognostic marker (Hirjak et al. 2016). Our results encourage the use of dimension reduction and clustering techniques in motor dysfunction studies across mental disorders. We have shown that patients with BD and SZ were set apart in each cluster in a similar proportion. There was no cluster characteristic for the specific psychiatric disorder. This result indicates similarities between those two disorders.

5. Conclusion

To our best knowledge, we are presenting the first data indicating the relationship between implicit motor learning and NSS and CSS in SZ and BD patients' groups. Lack of clusters predominantly represented by patients with the diagnosis of SZ or BD may refer to the model of schizophrenia-bipolar disorder boundary, pointing out the similarities between those two disorders.

Conflicts of interest

None to declare.

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Study was not funded

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References:

Bora, E., Akgül, Ö., Ceylan, D., Özerdem, A., 2018. Neurological soft signs in bipolar disorder in comparison to healthy controls and schizophrenia: A meta-analysis. Eur. Neuropsychopharmacol. 28, 1185–1193. https://doi.org/10.1016/j.euroneuro.2018.08.006

Bottmer, C., Bachmann, S., Pantel, J., Essig, M., Amann, M., Schad, L.R., Magnotta, V., Schröder, J., 2005. Reduced cerebellar volume and neurological soft signs in first-episode schizophrenia. Psychiatry Res. - Neuroimaging 140, 239–250. https://doi.org/10.1016/j.pscychresns.2005.02.011

Buchanan, R.W., Heinrichs, D.W., 1989. The Neurological Evaluation Scale (NES): a structured instrument for the assessment of neurological signs in schizophrenia. Psychiatry Res. 27, 335–350.

Chan, R.C.K., Xu, T., Heinrichs, R.W., Yu, Y., Wang, Y., 2010. Neurological soft signs in schizophrenia: a meta-analysis. Schizophr. Bull. 36, 1089–104. https://doi.org/10.1093/schbul/sbp011

Chrobak, A.A., Siuda-Krzywicka, K., Siwek, G.P., Arciszewska, A., Siwek, M., Starowicz-Filip, A., Dudek, D., 2015. Implicit motor learning in bipolar disorder. J. Affect. Disord. 174, 250–256. https://doi.org/10.1016/j.jad.2014.11.043

Chrobak, A.A., Siuda-Krzywicka, K., Siwek, G.P.G.P., Tereszko, A., Janeczko, W., Starowicz-Filip, A., Siwek, M., Dudek, D., 2017. Disrupted implicit motor sequence learning in schizophrenia and bipolar disorder revealed with ambidextrous Serial Reaction Time Task. Prog. Neuro-Psychopharmacology Biol. Psychiatry 79, 169–175. https://doi.org/10.1016/j.pnpbp.2017.06.025

Chrobak, A.A., Siuda, K., Biela, M., Arciszewska, A., Siwek, M., Pilecki, M.W., Dudek, D., 2014a. Convergence insufficiency with unilateral exophoria at near in schizophrenia and bipolar disorder - A preliminary study | Niewydolność konwergencji z jednostronnĄ egzoforiĄ do bliży w schizofrenii i chorobie afektywnej dwubiegunowej - Badania wstępne. Psychiatr. Pol. 48.

Chrobak, A.A., Siwek, G.P., Siuda-Krzywicka, K., Arciszewska, A., Starowicz-Filip, A., Siwek, M., Dudek, D., 2016. Neurological and cerebellar soft signs do not discriminate schizophrenia from bipolar disorder patients. Prog. Neuro-Psychopharmacology Biol. Psychiatry 4, 96–101. https://doi.org/10.1016/j.pnpbp.2015.07.009

Chrobak, A.A., Tereszko, A., Jeziorko, S., Siwek, M., Dudek, D., 2014b. Paradigms of procedural learning – a review of selected methods. Neuropsychiatry Neuropsychol. / Neuropsychiatr. i Neuropsychol.

Dazzan, P., Morgan, K.D., Chitnis, X., Suckling, J., Morgan, C., Fearon, P., McGuire, P.K., Jones, P.B., Leff, J., Murray, R.M., 2006. The structural brain correlates of neurological soft signs in healthy individuals. Cereb. Cortex 16, 1225–1231. https://doi.org/10.1093/cercor/bhj063

Flashman, L.A., Flaum, M., Gupta, S., Andreasen, N.C., 1996. Soft signs and neuropsychological performance in schizophrenia. Am. J. Psychiatry 153, 526–532. https://doi.org/10.1176/ajp.153.4.526

Hirjak, D., Thomann, P.A., Wolf, R.C., 2016. Reacknowledging a "motor dimension" will lead to biologically reliable phenotypes and innovative treatment strategies in mental disorders. Eur Neuropsychopharmacol. 26, 1253-1254. https://doi.org/10.1016/j.euroneuro.2016.04.005

Hüttlova, J., Kikinis, Z., Kerkovsky, M., Bouix, S., Vu, M.A., Makris, N., Shenton, M., Kasparek, T., 2014. Abnormalities in myelination of the superior cerebellar peduncle in patients with schizophrenia and deficits in movement sequencing. Cerebellum 13, 415–424. https://doi.org/10.1007/s12311-014-0550-y

Ivleva, E.I., Morris, D.W., Moates, A.F., Suppes, T., Thaker, G.K., Tamminga, C. a, 2010. Genetics and intermediate phenotypes of the schizophrenia--bipolar disorder boundary. Neurosci. Biobehav. Rev. 34, 897–921. https://doi.org/10.1016/j.neubiorev.2009.11.022

Jahn, T., Cohen, R., Hubmann, W., Mohr, F., Köhler, I., Schlenker, R., Niethammer, R., Schröder, J., 2006. The Brief Motor Scale (BMS) for the assessment of motor soft signs in

schizophrenic psychoses and other psychiatric disorders. Psychiatry Res. 142, 177–189. https://doi.org/10.1016/j.psychres.2002.12.002

Kim, D.-J., Kent, J.S., Bolbecker, A.R., Sporns, O., Cheng, H., Newman, S.D., Puce, A., O'Donnell, B.F., Hetrick, W.P., 2014. Disrupted Modular Architecture of Cerebellum in Schizophrenia: A Graph Theoretic Analysis. Schizophr. Bull. i, 1–11. https://doi.org/10.1093/schbul/sbu059

Kong, L., Herold, C.J., Cheung, E.F.C., Chan, R.C.K., Schröder, J., 2020. Neurological Soft Signs and Brain Network Abnormalities in Schizophrenia. Schizophr. Bull. 46, 562–571. https://doi.org/10.1093/schbul/sbz118

Kühn, S., Romanowski, A., Schubert, F., Gallinat, J., 2012. Reduction of cerebellar grey matter in Crus I and II in schizophrenia. Brain Struct. Funct. 217, 523–9. https://doi.org/10.1007/s00429-011-0365-2

Nissen, M., Bullemer, P., 1987. Attentional requirements of learning: evidence from performance measures. Cogn. Psychol. 19, 1–32.

Shinn, A.K., Roh, Y.S., Ravichandran, C.T., Baker, J.T., Öngür, D., Cohen, B.M., 2017. Aberrant Cerebellar Connectivity in Bipolar Disorder With Psychosis. Biol. Psychiatry Cogn. Neurosci. Neuroimaging 2, 438–448. https://doi.org/10.1016/j.bpsc.2016.07.002

Siegert, R.J., Weatherall, M., Bell, E.M., 2008. Is implicit sequence learning impaired in schizophrenia? A meta-analysis. Brain Cogn. 67, 351–9. https://doi.org/10.1016/j.bandc.2008.02.005

Storey, E., Tuck, K., Hester, R., Hughes, A., Churchyard, A., 2004. Inter-rater reliability of the International Cooperative Ataxia Rating Scale (ICARS). Mov. Disord. 19, 190–192. https://doi.org/10.1002/mds.10657

Thomann, P.A., Hirjak, D., Kubera, K.M., Stieltjes, B., Wolf, R.C., 2015. Neural network activity and neurological soft signs in healthy adults. Behav. Brain Res. 278, 514–519. https://doi.org/10.1016/j.bbr.2014.10.044

Trouillas, P., Takayanagi, T., Hallett, M., Currier, R.D., Subramony, S.H., Wessel, K., Bryer, A., Diener, H.C., Massaquoi, S., Gomez, C.M., Coutinho, P., Ben Hamida, M., Campanella, G., Filla, A., Schut, L., Timann, D., Honnorat, J., Nighoghossian, N., Manyam, B., 1997. International Cooperative Ataxia Rating Scale for pharmacological assessment of the cerebellar syndrome. The Ataxia Neuropharmacology Committee of the World Federation of Neurology. J. Neurol. Sci. 145, 205–11.

Tzvi, E., Zimmermann, C., Bey, R., Münte, T.F., Nitschke, M., Krämer, U.M., 2017. Cerebellar degeneration affects cortico-cortical connectivity in motor learning networks. NeuroImage Clin. 16, 66–78. https://doi.org/10.1016/j.nicl.2017.07.012

Varambally, S., Venkatasubramanian, G., Thirthalli, J., Janakiramaiah, N., 2006. Cerebellar and other neurological soft signs in antipsychotic-naïve schizophrenia 352–356. https://doi.org/10.1111/j.1600-0447.2006.0837.x

Venkatasubramanian, G., Jayakumar, P., Gandhi, B., Keshavan, M., 2008. Neuroanatomical correlates of neurological soft signs in antipsychotic-naive schizophrenia. Psychiatry Res. 164, 215–222.

Zhao, Q., Li, Z., Huang, J., Yan, C., Dazzan, P., Pantelis, C., Cheung, E.F.C., Lui, S.S.Y., Chan, R.C.K., 2014. Neurological soft signs are not "soft" in brain structure and functional networks: Evidence from ALE meta-analysis. Schizophr. Bull. 40, 626–641. https://doi.org/10.1093/schbul/sbt063
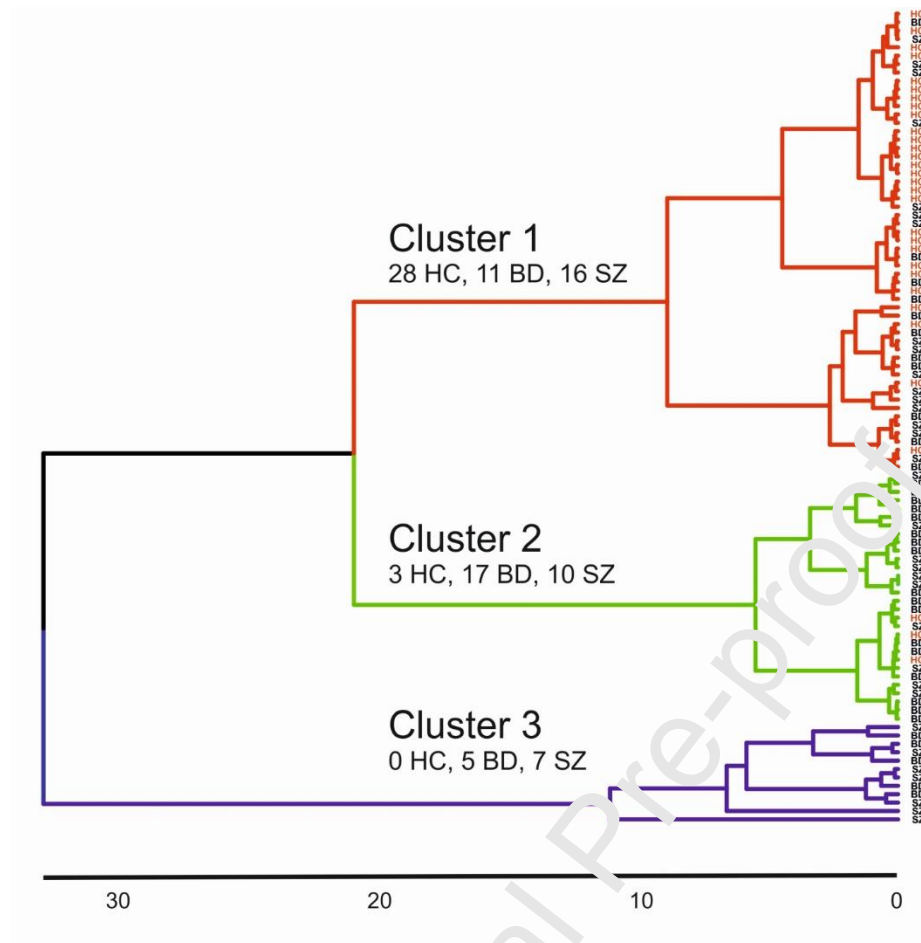
Fig S1. Dendrogram of cluster analysis performed with normalized main values of Serial Reaction Time Task. HC – healthy controls, BD – bipolar disorder, SZ – schizophrenia.

AAC – Conceptualization, Methodology, Investigation, Writing – Original Draft, Writing – Review & Editing, Supervision; KSK – Conceptualization, Methodology, Investigation, Writing – Review & Editing, Supervision. Software; ZS – Conceptualization, Methodology, Formal analysis, Investigation, Writing – Review & Editing, Supervision. Software, Visualization; GPS – Investigation, Writing – Review & Editing; BB – Writing – Original Draft, Writing – Review & Editing; AS – Writing – Original Draft, Writing – Review & Editing; AC – Writing – Original Draft, Writing – Review & Editing; AT – Investigation, Writing – Review & Editing; ASF – Writing – Review & Editing, Supervision; MF – Writing – Review & Editing, Supervision; TM – Writing – Review & Editing, Supervision; MS – Conceptualization, Investigation, Writing – Review & Editing, Supervision; DD – Conceptualization, Investigation, Writing – Review & Editing, Supervision

None to declare

Ethical Statement for Progress in Neuro-Psychopharmacology & Biological Psychiatry

I testify on behalf of all co-authors that our article submitted to NeuroPsychopharmacology & Biological Psychiatry:

Title: Relationship between neurological and cerebellar soft signs, and implicit motor learning in schizophrenia and bipolar disorder.

All authors: Adrian Andrzej Chrobak, Katarzyna Siuda-Krzywicka, Zbigniew Sołtys, Grzegorz Przemysław Siwek, Bartosz Bohaterewicz, Anna Sobczak, Anna Ceglarek, Anna Tereszko, Anna Starowicz-Filip, Magdalena Fąfrowicz, Tadeusz Marek, Marcin Siwek, Dominika Dudek

1) this material has not been published in whole or in part elsewhere;

2) the manuscript is not currently being considered for publication in another journal;

3) all authors have been personally and actively involved in substantive work leading to the manuscript, and will hold themselves jointly and individually responsible for its content.

Adrian Chrobak

- There are relationships between implicit motor learning and subtle motor deficits
- Patients clusterize according to the motor dysfunctions.
- There was no cluster characteristic for the specific psychiatric disorder.