Relationship between cerebellar impairments and lexicon retrieval in schizophrenia – preliminary study

Adrian Andrzej Chrobak, Michał Biela, Katarzyna Siuda, Marcin Siwek, Dominika Dudek, Maciej Wojciech Pilecki

Summary

Aim of the study. Investigation of relationship between cerebellar motor dysfunctions and language impairments connected with cerebellum during phonological and semantic fluency tasks and verb generation task in schizophrenic patients and healthy control group.

Subject or material and methods. 14 schizophrenic patients on olanzapine, clozapine or quetiapine treatment and 13 healthy volunteers were examined. Motor signs were assessed by using the
International Co-operative Ataxia Rating Scale (ICARS). Phonological and semantic fluency tasks were performed. All of the words were recorded and counted.

Results. Patients with schizophrenia revealed significantly higher ICARS mean score (12.21) than control group (3.92), and lower number of proper generated words in semantic fluency and verb generation tasks. Strong negative correlation ($r_s(13) = -0.71$, $p<0.01$) was found between ICARS total score and number of proper answers in verb generation task.

Discussion. Higher number of total ICARS score in schizophrenia patients in comparison to control group may suggest cerebellar impairments. There is disproportion between semantic and phonological fluency. Significant correlation between verb generation and cerebellar signs supports a hypothesis of cerebellum dysfunction during this task in schizophrenia patients.

Conclusions. Schizophrenic patients reveal impairments which may be connected with the cerebellum.

schizophrenia / verb generation / cerebellum / cognitive dysmetria

INTRODUCTION

Cognitive dysmetria hypothesis suggests that dysfunctions of the cerebellum and its loop connections with e.g. prefrontal cortex may cause impaired sequencing and coordination of sensorimotor and mental processes [1]. Growing number of evidence suggests that those dysfunctions may be involved in pathophysiology of schizophrenia [2][3]. MRI studies of patients with this disease reveals alterations of the cerebellum structure, such as smaller volume of the vermis and inferior posterior lobe [4] or conversely increased vermis volume along with increased cerebellar hemispheric volume asymmetry [5]. It is proposed that changes in the cerebellum volume may lead to disruption of activity in the cerebrum, which is important in development of schizophrenia [6].

Studies of Daskalakis et al. with a use of transcranial magnetic stimulation revealed that patients with schizophrenia demonstrate significant deficits in cerebellar inhibition in comparison with healthy subjects [7]. Post mortem studies reveal deficits also in the cellular level,

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growing number of evidence reports decrease in Purkinje cells and in GABAergic signaling in schizophrenia patients cerebellum (for review [8]). Interestingly it has been shown that developmental cerebellar anomalies may be a cause of schizophrenic symptoms in late adolescence [9].

Mentioned alterations correspond with clinical view of the patients - cerebellar motor symptoms are often observed during Romberg test and tandem gait [10]. Additionally, motor coordination deficits are negatively correlated with cerebellar white matter volume [11]. Furthermore, there have been found a significant inverse correlation between neurological soft signs scores (NSS) and right cerebellar hemisphere volume [12]. Presence of the cerebellar signs is often associated with poor premorbid adjustment, severe negative symptoms, smaller cerebellar tissue volume and greater cognitive impairment [10].

Traditionally cerebellar dysfunctions were tested during physical examination but growing number of scientific studies suggests that cerebellum takes part in higher mental functions [13-16], such as language processing [9]. Clinical studies on patients with cerebellar impairments have revealed language dysfunctions [17], especially in area of semantic access and verbal fluency.

Former studies have shown that cerebellar impairments could be assessed by performing neuropsychological test for lexicon retrieval, such as verbal fluency (phonemic and semantic) [18] or verb generation task [17]. Due to the fact that exploration of cognitive functions connected to cerebellum is a new field in neuroscience, data on impairment of lexical retrieval is limited. Studies on children that underwent excision of cerebellar tumors, especially with damage to the right cerebellar hemisphere, have revealed large verbal fluency impairments in this group [19]. Additionally, patients with cerebellar impairments i.e infarct in the right hemisphere has shown generation of incorrect and atypical responses during word generation tasks [17, 20]. Constituently to these findings, fMRI researches show cerebellum activation during those tasks in healthy volunteers [21-22]. The aim of our preliminary study was to verify if patients with schizophrenia with higher cerebellar signs scores, reflected in International Co-operative Ataxia Rating Scale (ICARS) score, will also reveal more impairments in language tasks connected to cerebellum dysfunctions, such as verbal fluency tasks and verb generation.

MATERIALS AND METHODS

During the preliminary investigation we examined 14 patients with schizophrenia, 5 women and 9 men, with mean age 41.5 years (SD= 11.48, range 25–61).

Inclusion criteria for patients were as follow: 1) meeting the criteria of ICD-10 and DSM-IVTR of schizophrenia, 2) treatment with antipsychotic drugs from the group of dibenzoxazepine (olanzapine, clozapine, quetiapine) as monotherapy (Tab. 1), 3) state of full remission of psychotic symptoms.

Table 1. Patients' age and medication

N	Medication	Daily dosage	Age
1	olanzapine	10mg	40
2	olanzapine	15mg	52
3	quetiapine	600mg	57
4	olanzapine	15mg	45
5	olanzapine	20mg	52
6	olanzapine	10mg	61
7	olanzapine	5mg	44
8	olanzapine	10mg	25
9	clozapine	600mg	39
10	olanzapine	10mg	36
11	quetiapine	800mg	44
12	clozapine	150mg	25
13	olanzapine	10mg	27
14	quetiapine	700mg	34

Exclusion criteria for patients: 1) alcohol or drug addiction, 2) severe, acute and chronic neurological and somatic diseases, 3) severe personality disorders or depression, 4) different medication from this mentioned above.

Healthy control group consisted of 13 volunteers, 7 women and 6 men, with mean age 44.46 years (SD = 10.81, range 22 – 57), recruited from research group's social network, matched for sex, age and level of education with patients. Exclusion criteria in control group were the same as those for patients, only the criterion of no psychiatric condition in the past and no family history of psychiatric or neurological disorders was

added. All of the healthy participants signed informed written consent to the assessment. The study was approved by the Jagiellonian University Bioethics Committee.

The investigation consisted of four tasks: neurological assessment, semantic fluency task, phonological fluency task and verb generation task.

Neurological assessment

The level of neurological disturbances were assessed using the International Co-operative Ataxia Rating Scale [23]. ICARS is a 100-point scale which is divided into four parts:

1. gait and posture subscore (34 points)
2. kinetic functions subscore (52 points)
3. dysarthria subscore (8 points)
4. oculomotor subscore (6 points)

In the first part of ICARS (gait and posture subscore), walking capacities, gait speed, standing capacities, spread of feet in natural position, body swaying with feet together (with eyes open and separately with eyes closed) and quality of sitting position are taken into account.

The second part consists of knee-tibia test, finger-nose test (both tremor and decomposition of the movement), finger-finger test, alternating movements and Archimedes spiral drawing. Knee-tibia test, finger-nose test and alternating movements test were all done separately for left and right limb.

Dysarthria score assesses fluency and clarity of speech whilst oculomotor part consists of three parts: gaze-evoked nystagmus, ocular pursuit abnormalities, and dysmetria of the saccade.

For each test the subject can get specified amount of points in order to properly assess the stage of disorders. For example for "walking capacities test" patient can get maximally 8 points but for "abnormalities of the ocular pursuit" only 2.

This scale needs around 20 minutes to administer and it is a relatively easy instrument to assess wide range of ataxia severities as a sum [23], but it also can be used to compare the results of four subscores.

Semantic fluency task

The participants were given 60 seconds to generate as many animals as they can think of.

Produced words were digitally recorded, then counted and analyzed in terms of adequacy of

the word and number of repetitions. Repeated animals were counted as one and in case of any doubts, the existence of questionable animal was precisely checked.

Phonological fluency task

The participants were given a letter of the alphabet (in this investigation the letter "k" has been used) and had 60 seconds to generate as many words as possible starting from this letter.

All words were properly recorded, counted and analyzed in terms of adequacy of the word and number of repetitions. Repeated words were counted as one and in the case of any doubts, the existence of questionable word was precisely checked.

Verb generation

In this trial the 20 nouns were respectively presented visually, on a computer monitor, and in audio format via headphones. Participants were instructed to say within 3 seconds a verb that described either what the object does or what you do with the object. For all participants the same nouns in the same order were presented. All responses were recorded and analyzed in terms of adequacy (if the generated word was the verb and if it described adequately presented nouns).

RESULTS

Statistical analysis was performed using the SPSS software. In the control group distribution of scores in ICARS scale D (13) = 0.25, p = 0.027 and verb generation task D (13) = 0,36 , p < 0.001 were both significantly non-normal. In the patient group the distribution of scores in verb generation task occurred to be significantly non normal (D (14) = 0.26, p = 0.014). Due to the non-normality of those distributions, U-Mann Whitney test was performed in order to check the differences between groups (Chart 1, Chart 2 – *next page*).

One-tailed U Mann Whitney test revealed significant between group differences in scores in: ICARS scale (U=15.5, z=-3.69, p<0.001, r=-0.71), semantic verbal fluency task (U=33, z=-2.83,
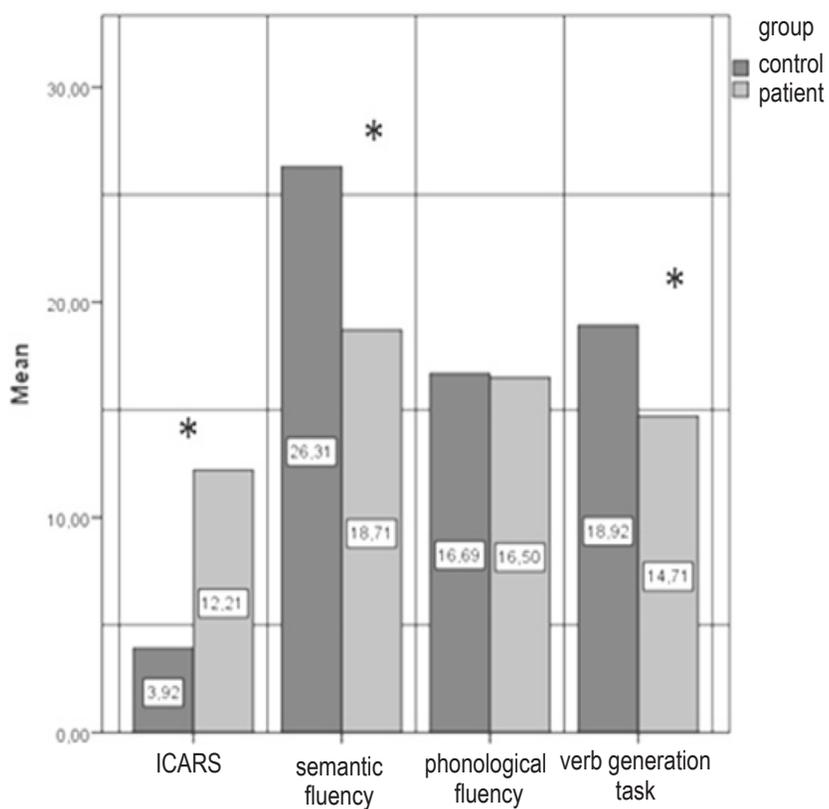
Chart 1. Mean tasks' results for controls and patients group.
* = significant difference (p < 0.05) on paired one-tailed U Mann Whitney test
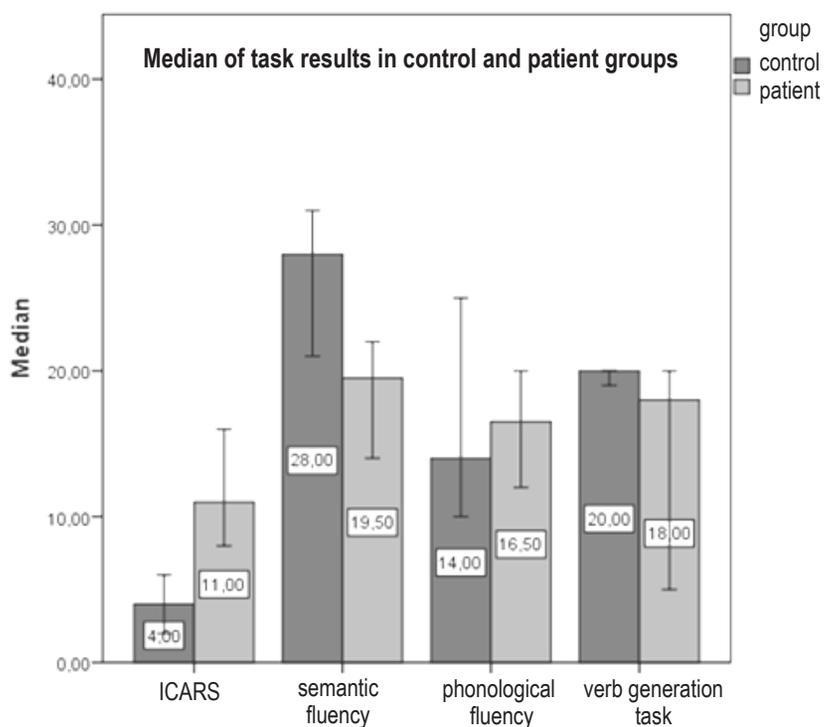
Chart 2. Median and standard deviation of performances in both control
and patients group

p=0.002, r= -0.54) and verb generation task (U=54, z= -1.91, p=0.029, r= -0.37).Difference in scores in formal fluency task appeared to be statistically insignificant (U=87, z= -0.2, p=0.429). Additionally, in ICARS scale means of each subscale was also calculated (Table 2).

Table 2. Mean results for each subscales of ICARS scale for patients and control group

	Patients		Control group	
	Mean ± SD	Median	Mean ± SD	Median
All	12.21 ± 5.56	11	3.92 ± 1.89	4
Posture and gait	3.14 ± 1.99	3	2.23 ± 1.01	2
Kinetic score	6.71 ± 4.16	6.5	0.85 ± 1.14	0
Dysarthria score	0.5 ± 0.85	0	0.23 ± 0.60	0
Oculomotor score	1.86 ± 1.46	1.5	0.62 ± 0.51	1

Due to non-normality of data distribution, Spearman two tailed correlation test was performed. In patient group, number of words generated properly in verb generation task correlated significantly with ICARS scale scores (rs(13) = -0.71, p<0.01).

DISCUSSION

Patients with schizophrenia revealed more than three times higher ICARS total score than control group, showing significant higher rate of cerebellar motor dysfunctions. Patients under antipsychotic treatment (olanzapine, quetiapine, or clozapine) presented greater total score than neuroleptic naive patients in previous study [24]. Varambally et al. have examined 32 schizophrenia patients and healthy controls using ICARS and NSS. They revealed that differences in Kinetic and Dysarthria subscales were significant, accounting for 78% of classification. Our results showed significant differences between patients and healthy controls in all of the subscores and similar proportions of cerebellar signs in (Kinetic > Posture and gait > Oculomotor > Dysarthria scores). Because there were no studies on cerebellum signs on patients with schizophrenia under similar treatment to ours, future analysis will require comparison with a group of patients with other disease under the same medication. Nevertheless presence of cerebellar symptoms in

schizophrenia patients is significant and it corresponds with other studies. Our preliminary data showed that there is disproportion between total numbers of generated words in fluency tasks in patients diagnosed with schizophrenia. Significant lower score during semantic fluency in comparison with phonemic fluency was also observed in previous studies [25-27] During 2 min fluency task of switching between words that begin with F and animals Gourovitch et al. showed that control group revealed more words during semantic versus phonologic fluency. Authors suggest that results may indicate dysfunction of frontal and temporoparietal areas of the brain and the breakdown of semantic information processing beyond "executive" search and retrieval [25]. Goldberg et al. indicated also that disorganization of semantic system is associated with thought disorder [26]. Bozikas et al. analyzed total word production, number of semantic clusters of words and the number of switches in both tasks and they have concluded that impairment in semantic fluency in schizophrenia patients is caused by differential deficits only in clustering. Those results suggest that the origin of lower performance in verbal fluency task may be due to disorganization of thoughts rather than to impaired access and retrieval from semantic storage [27]. Consistently, recent study using singular value decomposition to analyze the outcome of different clustering techniques has revealed that patients with schizophrenia show less coherent semantic clustering for high and low-frequency words. This suggests that impaired automatic activation of semantic information may be one of the major deficits in schizophrenia [28]. Patients with cerebellar dysfunctions are less likely to benefit from category structure in tasks requiring memorizing lists of words [29-31]. This phenomenon may also be related to the decrease of performance in semantic fluency. Lack of correlation between this task and ICARS total score does not suggest directly connections with cerebellum impairment.

Our preliminary study revealed strong negative correlation between severity of cerebellar motor dysfunctions and a number of properly generated verbs. Previous studies have indicated neural structures involved in word selection

which occurs in verb generation task. Left inferior frontal cortex (IFC) is active during semantic retrieval task including selection of one word among several possibilities [32, 33]. Anterior cingulate cortex (ACC) was proposed to play a role in monitoring the occurrence of conflict between rivaling candidate responses [34]. Cerebellum was also found to be key structure participating in verb generation task [35]. Especially right lateral area of the cerebellum is active during non-motor language processes [36]. Cerebellum activations have been concomitant with the contralateral left frontal lobe suggesting involvement of fronto-cerebellar pathways in language tasks [37, 38]. Consistently, more recent studies show activation of HVI/Crus 1 of the right cerebellar hemisphere and ventrocaudal parts of dentate nucleus in verb generation task [22, 21].

Studies of word production deficits in schizophrenia have indicated that impairments in verb generation tasks may be caused by fronto-cerebellar dysfunction [31]. Our findings indirectly supports a hypothesis that cerebellum dysfunction may be one of the causal component in impairments during this task in schizophrenia patients and requires attention in future studies. They are also consistent with findings of attenuated cerebellar structure in this disease. It has been shown that higher scores of motor coordination subscores of NSS are correlated negatively with white matter structure of the cerebellum. Also total NSS scores are associated with altered cerebello-thalamo-cortical network [11] and interestingly with mentioned right cerebellar hemisphere volume, involved in language processesing [39].

In our opinion, collected data suggest a promising direction in our research. To our knowledge there are no recent fMRI studies of verb generation in schizophrenia patients, but we speculate that our findings correspond with mentioned cerebellar abnormalities. The direction of observed correlation between verb generation task and ICARS scale is in line with our hypothesis of relationships between language skills and cortico-thalamo-cerebellar circuits' impairment in case of schizophrenia. Moreover, significant differences between control and patient groups in semantic fluency task is in line with theory of impaired semantic clustering in schizophrenia, described in the introduction of our paper. We are fully aware of strong limitations of our study, such as small, non-randomized sample and lack of psychiatric assessment of examined patients. In future projects larger group of patients, PANSS assessment and fMRI analysis shall be provided in order to properly understand our preliminary results.

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