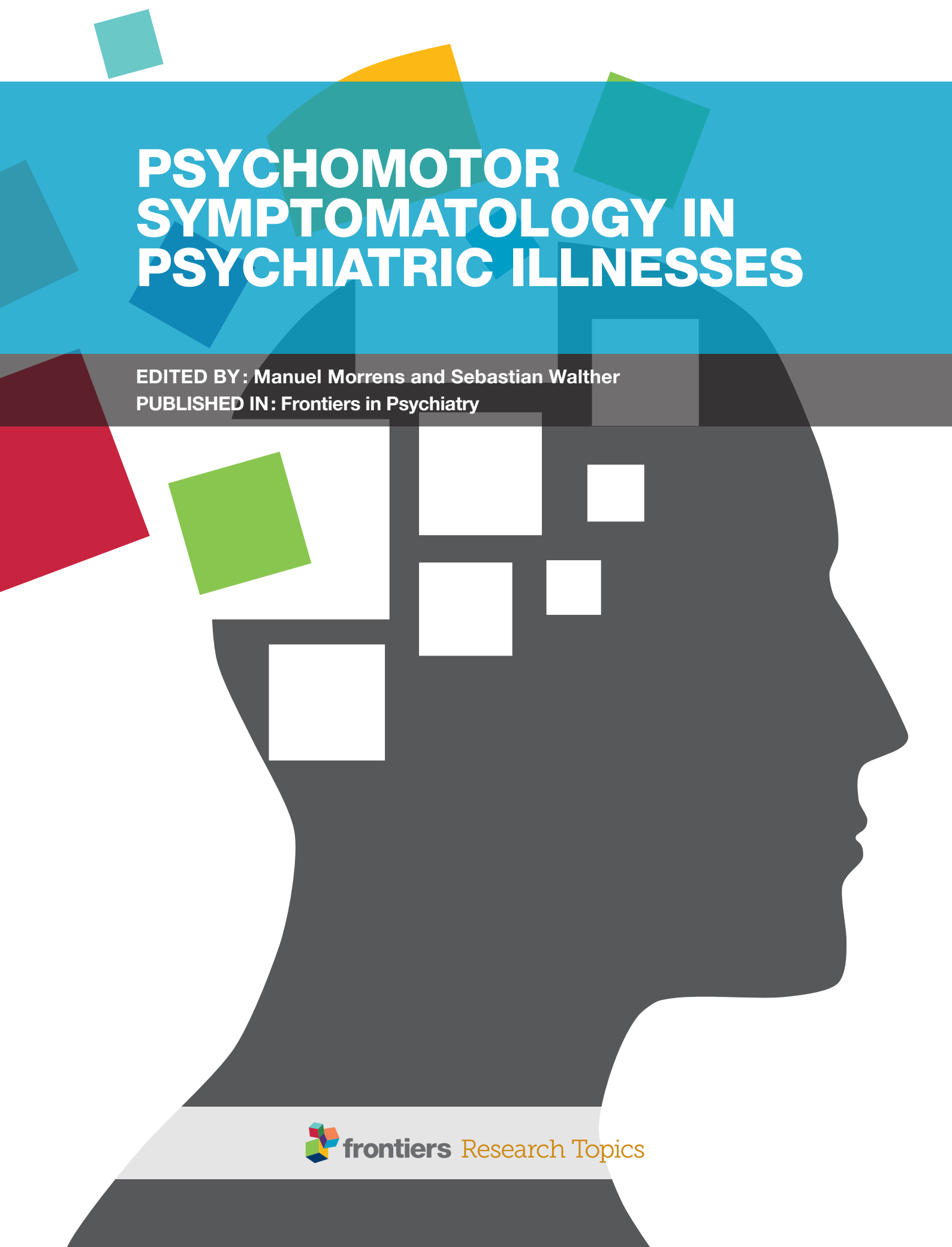
PSYCHOMOTOR SYMPTOMATOLOGY IN PSYCHIATRIC ILLNESSES

EDITED BY: Manuel Morrens and Sebastian Walther

PUBLISHED IN: Frontiers in Psychiatry



frontiers Research Topics

frontiers

ISSN 1664-8714
ISBN 978-2-88919-725-5
DOI 10.3389/978-2-88919-725-5

About Frontiers

Frontiers is more than just an open-access publisher of scholarly articles: it is a pioneering approach to the world of academia, radically improving the way scholarly research is managed. The grand vision of Frontiers is a world where all people have an equal opportunity to seek, share and generate knowledge. Frontiers provides immediate and permanent online open access to all its publications, but this alone is not enough to realize our grand goals.

Frontiers Journal Series

The Frontiers Journal Series is a multi-tier and interdisciplinary set of open-access, online journals, promising a paradigm shift from the current review, selection and dissemination processes in academic publishing. All Frontiers journals are driven by researchers for researchers; therefore, they constitute a service to the scholarly community. At the same time, the Frontiers Journal Series operates on a revolutionary invention, the tiered publishing system, initially addressing specific communities of scholars, and gradually climbing up to broader public understanding, thus serving the interests of the lay society, too.

Dedication to quality

Each Frontiers article is a landmark of the highest quality, thanks to genuinely collaborative interactions between authors and review editors, who include some of the world's best academicians. Research must be certified by peers before entering a stream of knowledge that may eventually reach the public - and shape society; therefore, Frontiers only applies the most rigorous and unbiased reviews.
Frontiers revolutionizes research publishing by freely delivering the most outstanding research, evaluated with no bias from both the academic and social point of view.
By applying the most advanced information technologies, Frontiers is catapulting scholarly publishing into a new generation.

What are Frontiers Research Topics?

Frontiers Research Topics are very popular trademarks of the Frontiers Journals Series: they are collections of at least ten articles, all centered on a particular subject. With their unique mix of varied contributions from Original Research to Review Articles, Frontiers Research Topics unify the most influential researchers, the latest key findings and historical advances in a hot research area! Find out more on how to host your own Frontiers Research Topic or contribute to one as an author by contacting the Frontiers Editorial Office: **researchtopics@frontiersin.org**

PSYCHOMOTOR SYMPTOMATOLOGY IN PSYCHIATRIC ILLNESSES

Topic Editors:
Manuel Morrens, University of Antwerp, Belgium
Sebastian Walther, University Hospital of Psychiatry Bern, Switzerland

Psychomotor symptoms are those symptoms that are characterized by deficits in the initiation, execution and monitoring of movements, such as psychomotor slowing, catatonia, neurological soft signs (NSS), reduction in motor activity or extrapyramidal symptoms (EPS). These symptoms have not always received the attention they deserve although they can be observed in a wide range of psychiatric illnesses, including mood disorders, psychotic disorders, anxiety disorders, pervasive developmental disorders and personality disorders. Nevertheless, these symptoms seem to have prognostic value on clinical and functional outcome in several pathologies.

In the late 19th century, the founding fathers of modern psychiatry (including Kahlbaum, Wernicke, Kraepelin and Bleuler) had a strong focus on psychomotor abnormalities in their description and definitions of psychiatric illnesses and systematically recognized these as core features of several psychiatric pathologies. Nevertheless, emphasis on these symptoms has reduced substantially since the emergence of psychopharmacology, given the association between antipsychotics or antidepressants and medication-induced motor deficits. This has resulted in the general idea that most if not all psychomotor deficits were merely side effects of their treatment rather than intrinsic features of the illness.

Yet, the last two decades a renewed interest in these deficits can be observed and has yielded an exponential growth of research into these psychomotor symptoms in several psychiatric illnesses. This recent evolution is also reflected in the increased appreciation of these symptoms in the DSM-5.

As a result of this increased focus, new insights into the clinical and demographical presentation, the etiology, the course, the prognostic value as well as treatment aspects of psychomotor symptomatology in different illnesses has emerged. Still, many new questions arise from these findings.

This research topic is comprised of all types of contributions (original research, reviews, and opinion piece) with a focus on psychomotor symptomatology in a psychiatric illness, especially research focusing on one or more of the following topics: the clinical presentation of

the psychomotor syndrome; the course through the illness; the diagnostical specificity of the syndrome; the underlying neurobiological or neuropsychological processes; new assessment techniques; pharmacological or non-pharmacological treatment strategies.

Citation: Morrens, M., Walther, S., eds. (2015). Psychomotor Symptomatology in Psychiatric Illnesses. Lausanne: Frontiers Media. doi: 10.3389/978-2-88919-725-5

Table of Contents

frontiers in Psychiatry

EDITORIAL
published: 01 June 2015
doi: 10.3389/fpsyt.2015.00081

Editorial: Psychomotor symptomatology in psychiatric illnesses

Sebastian Walther[1]* *and Manuel Morrens*[2]

[1] University Hospital of Psychiatry, University of Bern, Bern, Switzerland, [2] Collaborative Antwerp Psychiatric Research Institute, University of Antwerp, Antwerp, Belgium

Keywords: schizophrenia, affective disorders, ADHD, Alzheimer's disease, autism spectrum disorders

In this research topic, we have gathered articles focusing on the psychomotor component of psychiatric disorders. Indeed, motor symptoms remain as an important dimension of psychopathology that can be assessed by objective means. Particularly, in major depressive disorder and schizophrenia, motor signs have been acknowledged from the very early descriptions (1–3). But, psychomotor abnormalities have also been demonstrated in other psychiatric disorders.

This research topic included nine original articles, four reviews, three opinion papers, and one mini-review. Catatonia has been subjected to two reviews (4, 5) and one investigation of its prevalence among acutely hospitalized patients (6). Neurological soft signs have been shown to occur in autism spectrum disorders (7), in Alzheimer's disease (8) and have been reviewed for their predictive validity in the course of schizophrenia (9). Fine motor tasks demonstrated that motor learning was preserved in schizophrenia despite cognitive and motor impairments (10, 11). In addition, psychomotor retardation was found in depressed elderly more than in elderly without depression (12). A neuroimaging study explored the cingulate motor area in motor retardation in major depression (13). The functional neuroanatomy of motor retardation in depression was also subjected to a mini-review (14). The topography of the cerebellum has been suggested as interesting focus of study to disentangle motor and cognitive functions in schizophrenia spectrum disorders (15). Two studies using actigraphy reported on gross motor activity in the course of schizophrenia (16, 17). Finally, Gawrilow and colleagues summarized the importance of motor activity in ADHD (18).

Currently, ambiguous terminology and definitions hamper research on psychomotor phenomena. In addition, some studies focus exclusively on single signs probably missing the complete picture. Therefore, we have tried to put forward a systematic approach to study psychomotor phenomena in psychotic disorders (19). In addition, van Harten and colleagues have proposed to consider movement disorders as non-mental signs of psychotic disorders just as psychiatric symptoms are classified as non-motor signs in idiopathic movement disorders (20).

One example of ongoing debate is the current discussion on the catatonia syndrome. Depending on the criteria applied, prevalence rates differ substantially (6, 21, 22), challenging the specificity of assessment methods. Despite the fact that the syndrome is quite remarkable, there is not much of a common ground in the literature as to what catatonia should be defined as. Clearly, this ambiguity of definitions has contributed to the scarcity of descriptive and interventional studies in the catatonia syndrome.

Another important field of research is the outcome of interventions in motor symptoms. Further research needs to clarify whether the motor dimension in psychiatric disorders is properly ameliorated by treating the underlying disorder or whether specific therapeutic options are required. The former would call for generalized therapies in depression, schizophrenia, or autism. The latter would instead require searching for new therapeutic targets, such as in movement

OPEN ACCESS

Edited and reviewed by:
Mihaly Hajos, Yale University School of Medicine, USA

***Correspondence:**
Sebastian Walther
walther@puk.unibe.ch

Specialty section:
This article was submitted to Schizophrenia, a section of the journal Frontiers in Psychiatry

Received: *08 April 2015*
Accepted: *17 May 2015*
Published: *01 June 2015*

Citation:
Walther S and Morrens M (2015) Editorial: Psychomotor symptomatology in psychiatric illnesses. Front. Psychiatry 6:81. doi: 10.3389/fpsyt.2015.00081

disorders known in neurology. Clearly defined psychomotor disturbances may benefit from deep brain stimulation of the subthalamic nucleus (23), pedunculopontine nucleus (24), or other targets such as the reward system (25). Likewise, non-invasive brain stimulation may become a treatment option in those psychomotor disturbances related to dysfunctions in cortical motor areas.

Taken together, clarified terminology, increased awareness, and improved assessment methods will help psychomotor symptoms to become an important objective dimension of psychopathology that is informative on underlying neuropathology and longitudinal course. These transitions in psychiatric assessment will also allow for more specialized interventions for psychomotor symptoms.

References

1. Sobin C, Sackeim HA. Psychomotor symptoms of depression. *Am J Psychiatry* (1997) **154**(1):4–17. doi:10.1176/ajp.154.1.4
2. Walther S, Strik W. Motor symptoms and schizophrenia. *Neuropsychobiology* (2012) **66**(2):77–92. doi:10.1159/000339456
3. Morrens M, Hulstijn W, Sabbe B. Psychomotor slowing in schizophrenia. *Schizophr Bull* (33) (4):1038–53. doi:10.1093/schbul/sbl051
4. Dhossche DM. Decalogue of catatonia in autism spectrum disorders. *Front Psychiatry* (2014) **5**:157. doi:10.3389/fpsyt.2014.00157
5. Sienaert P, Dhossche DM, Vancampfort D, De Hert M, Gazdag G. A clinical review of the treatment of catatonia. *Front Psychiatry* (2014) **5**:181. doi:10.3389/fpsyt.2014.00181
6. Stuivenga M, Morrens M. Prevalence of the catatonic syndrome in an acute inpatient sample. *Front Psychiatry* (2014) **5**:174. doi:10.3389/fpsyt.2014.00174
7. Hirjak D, Wolf RC, Koch SC, Mehl L, Kelbel JK, Kubera KM, et al. Neurological abnormalities in recent-onset schizophrenia and Asperger-syndrome. *Front Psychiatry* (2014) **5**:91. doi:10.3389/fpsyt.2014.00091
8. Urbanowitsch N, Degen C, Toro P, Schroder J. Neurological soft signs in aging, mild cognitive impairment, and Alzheimer's disease – the impact of cognitive decline and cognitive reserve. *Front Psychiatry* (2015) **6**:12. doi:10.3389/fpsyt.2015.00012
9. Bachmann S, Degen C, Geider FJ, Schroder J. Neurological soft signs in the clinical course of schizophrenia. *Front Psychiatry* (2014) **5**:185. doi:10.3389/fpsyt.2014.00185
10. De Picker LJ, Cornelis C, Hulstijn W, Dumont G, Fransen E, Timmers M, et al. Stable schizophrenia patients learn equally well as age-matched controls and better than elderly controls in two sensorimotor rotary pursuit tasks. *Front Psychiatry* (2014) **5**:165. doi:10.3389/fpsyt.2014.00165
11. Cornelis C, De Picker LJ, Hulstijn W, Dumont G, Timmers M, Janssens L, et al. Preserved learning during the Symbol Digit Substitution Test in patients with schizophrenia, age-matched controls and elderly. *Front Psychiatry* (2014) **5**:189. doi:10.3389/fpsyt.2014.00189
12. Beheydt LL, Schrijvers D, Docx L, Bouckaert F, Hulstijn W, Sabbe BG. Psychomotor retardation in untreated depressed elderly. *Front Psychiatry* (2014) **5**:196. doi:10.3389/fpsyt.2014.00196
13. Liberg B, Klauser P, Harding IH, Adler M, Rahm C, Lundberg J, et al. Functional and structural alterations in the cingulate motor area relate to decreased fronto-striatal coupling in major depressive disorder with psychomotor disturbances. *Front Psychiatry* (2014) **5**:176. doi:10.3389/fpsyt.2014.00176
14. Liberg B, Rahm C. The functional anatomy of psychomotor disturbances in major depressive disorder. *Front Psychiatry* (2015) **6**:34. doi:10.3389/fpsyt.2015.00034
15. Bernard JA, Mittal VA. Cerebellar-motor dysfunction in schizophrenia and psychosis-risk: the importance of regional cerebellar analysis approaches. *Front Psychiatry* (2014) **5**:160. doi:10.3389/fpsyt.2014.00160
16. Walther S, Stegmayer K, Horn H, Razavi N, Müller TJ, Strik W. Physical activity in schizophrenia is higher in the first episode than in subsequent ones. *Front Psychiatry* (2014) **5**:191. doi:10.3389/fpsyt.2014.00191
17. Walther S, Stegmayer K, Horn H, Rampa L, Razavi N, Muller TJ, et al. The longitudinal course of gross motor activity in schizophrenia – within and between episodes. *Front Psychiatry* (2015) **6**:10. doi:10.3389/fpsyt.2015.00010
18. Gawrilow C, Kuhnhausen J, Schmid J, Stadler G. Hyperactivity and motoric activity in ADHD: characterization, assessment, and intervention. *Front Psychiatry* (2014) **5**:171. doi:10.3389/fpsyt.2014.00171
19. Morrens M, Docx L, Walther S. Beyond boundaries: in search of an integrative view on motor symptoms in schizophrenia. *Front Psychiatry* (2014) **5**:145. doi:10.3389/fpsyt.2014.00145
20. van Harten PN, Backker R, Mentzel C, Tijssen M, Tenback DE. Movement disorders and psychosis, a complex marriage. *Front Psychiatry* (2014) **5**:190. doi:10.3389/fpsyt.2014.00190
21. Wilson JE, Niu K, Nicolson SE, Levine SZ, Heckers S. The diagnostic criteria and structure of catatonia. *Schizophr Res* (2015) **164**(1–3):256–62. doi:10.1016/j.schres.2014.12.036
22. Jaimes-Albornoz W, Serra-Mestres J. Prevalence and clinical correlations of catatonia in older adults referred to a liaison psychiatry service in a general hospital. *Gen Hosp Psychiatry* (2013) **35**(5):512–6. doi:10.1016/j.genhosppsych.2013.04.009
23. Castrioto A, Lhommee E, Moro E, Krack P. Mood and behavioural effects of subthalamic stimulation in Parkinson's disease. *Lancet Neurol* (2014) **13**(3):287–305. doi:10.1016/S1474-4422(13)70294-1
24. Morita H, Hass CJ, Moro E, Sudhyadhom A, Kumar R, Okun MS. Pedunculopontine nucleus stimulation: where are we now and what needs to be done to move the field forward? *Front Neurol* (2014) **5**:243. doi:10.3389/fneur.2014.00243
25. Schlaepfer TE, Bewernick BH, Kayser S, Hurlemann R, Coenen VA. Deep brain stimulation of the human reward system for major depression – rationale, outcomes and outlook. *Neuropsychopharmacology* (2014) **39**(6):1303–14. doi:10.1038/npp.2014.28

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in PSYCHIATRY

ORIGINAL RESEARCH ARTICLE
published: 03 December 2014
doi: 10.3389/fpsyt.2014.00174

Prevalence of the catatonic syndrome in an acute inpatient sample

Mirella Stuivenga*[1] *and Manuel Morrens*[1,2]

[1] *Collaborative Antwerp Psychiatric Research Institute (CAPRI), University of Antwerp, Antwerp, Belgium*
[2] *Psychiatric Center Brothers Alexians, Boechout, Belgium*

Edited by:
Mihaly Hajos, Yale University School of Medicine, USA

Reviewed by:
Bernhard J. Mitterauer, Volitronics-Institute for Basic Research Psychopathology and Brain Philosophy, Austria
Pascal Sienaert, Universitair Psychiatrisch Centrum KU Leuven, Belgium

***Correspondence:**
Manuel Morrens, Collaborative Antwerp Psychiatric Institute (CAPRI), University of Antwerp, Campus Drie Eiken, Universiteitsplein 1, Antwerp B-2610, Belgium
e-mail: manuel.morrens@uantwerpen.be

Objective: In this exploratory open label study, we investigated the prevalence of catatonia in an acute psychiatric inpatient population. In addition, differences in symptom presentation of catatonia depending on the underlying psychiatric illness were investigated.

Methods: One hundred thirty patients were assessed with the Bush–Francis Catatonia Rating Scale (BFCRS), the Positive and Negative Syndrome Scale, the Young Mania Rating Scale, and the Simpson–Angus Scale. A factor analysis was conducted in order to generate six catatonic symptom clusters. Composite scores based on this principal component analysis were calculated.

Results: When focusing on the first 14 items of the BFCRS, 101 patients (77.7%) had at least 1 symptom scoring 1 or higher, whereas, 66 patients (50.8%) had at least 2 symptoms. Interestingly, when focusing on the DSM-5 criteria of catatonia, 22 patients (16.9%) could be considered for this diagnosis. Furthermore, different symptom profiles were found, depending on the underlying psychopathology. Psychotic symptomatology correlated strongly with excitement symptomatology ($r = 0.528$, $p < 0.001$) and to a lesser degree with the stereotypy/mannerisms symptom cluster ($r = 0.289$; $p = 0.001$) and the echo/perseveration symptom cluster ($r = 0.185$; $p = 0.035$). Similarly, manic symptomatology correlated strongly with the excitement symptom cluster ($r = 0.596$; $p < 0.001$) and to a lesser extent with the stereotypy/mannerisms symptom cluster ($r = 0.277$; $p = 0.001$).

Conclusion: There was a high prevalence of catatonic symptomatology. Depending on the criteria being used, we noticed an important difference in exact prevalence, which makes it clear that we need clear-cut criteria. Another important finding is the fact that the catatonic presentation may vary depending on the underlying pathology, although an unambiguous delineation between these catatonic presentations cannot be made. Future research is needed to determine diagnostical criteria of catatonia, which are clinically relevant.

Keywords: catatonia, psychomotor, acute psychiatric admissions, classification, schizophrenia, mood disorders

INTRODUCTION

Catatonia is a psychomotor symptom cluster characterized by a heterogeneous group of mental, motor, vegetative, and behavioral signs. The recognition of catatonia is essential since it is a syndrome that can be effectively and rapidly relieved in most cases. Whereas, the pathophysiology of catatonia is still unknown, it is clear that the psychomotor syndrome results from many etiologies (1).

Although some critics have suggested the syndrome is much more uncommon than a century ago or may even be disappearing, catatonia is still highly prevalent (2). Whereas early investigators reported catatonia in 20–50% of the schizophrenic patients (3, 4), contemporary literature demonstrates the presence of catatonia in 4–15% of schizophrenia patients (5–8). In acutely ill psychiatric inpatients higher estimates are reported, ranging between 5 and 20% (9, 10).

Most recently, the DSM-5 rightfully loosened the association between schizophrenia and catatonia that was predominant in its preceding editions and now recognizes that catatonia can be induced by different disorders (11). In the study of Pommepuy and Januel, including 607 catatonic patients, there was an average of 30.9% of all patients with a primary diagnosis of schizophrenia, whereas 43% of the patients had a mood disorder (12). The review of Caroff and colleagues shows similar results (13). Among patients with a mood disorder, catatonia can be seen in patients with a bipolar disorder with a percentage of 17–47% in mania and 0–20% in patients with a depressive episode (14, 15). In a study including patients with an unipolar depressive disorder 20% of the patients met the criteria for catatonia (16).

There are reasons to believe that the profile of catatonic symptomatology may depend on the underlying pathology (15, 17). Krüger and colleagues demonstrated that catatonia in schizophrenia was mainly characterized by abnormal movements, stereotypies, mannerisms, catalepsy, negativism, automatic obedience, and waxy flexibility, whereas, catatonic excitation was more associated with mania and catatonic inhibition more with depression (15). This notion is very intriguing since it can both

have diagnostical and therapeutical implications and give clues toward future research on the underlying pathophysiology of the psychomotor syndrome.

In the present study, prevalence of catatonia in an acute psychiatric inpatient population was investigated. In addition, differences in symptom presentation of catatonia depending on the underlying psychiatric illness were investigated.

MATERIALS AND METHODS

STUDY DESIGN

In an exploratory open label study design, each patient admitted to a psychiatric intensive ward during a period of 12 months was assessed for catatonic and clinical symptomatology. The patients admitted to this department were experiencing the most acute phase of a mental illness. The department is for men and women over the age of 18 year who require a period of psychiatric intensive care. The assessments were conducted on the first day of admission in the hospital. There were no exclusion criteria for participation. All of the 130 patients who were admitted to the psychiatric intensive ward were included in the study.

PARTICIPANTS

A total group of 130 patients (female: $n = 50$; 38.5%) were tested after admission on an acute psychiatric enclosed ward. The mean age was 40.5 years (SD = 13.9; range 18–76). More than half of our patient group had a psychotic illness as a primary illness ($n = 67$; 51.5%) including 26 patients (20.0%) with schizophrenia (amongst which 3 patients with a diagnosed catatonic subtype) and 35 patients with a psychotic illness not otherwise specified (26.9%). The second most common primary diagnosis ($n = 16$; 12.3%) was a bipolar disorder, followed by substance abuse disorders ($n = 14$; 10.8%). Major depressive disorder was the main diagnosis in six patients (4.6%). Similarly, six patients received a diagnosis of personality disorder (4.6%).

Antipsychotics were taken by 56.9% of the patients ($n = 74$). Twenty-six patients (20.0%) took at least 1 first generation antipsychotic (FGA), whereas 64 patients (49.2%) took a second generation antipsychotic (SGA), 4 patients were taking lithium (3.1%), whereas 12 patients took anti-epileptics (9.2%) at the time of testing. Antidepressants were administered to 30.8% of the patients at the time of testing [SSRI ($n = 17$); SNRI ($n = 10$); TCA ($n = 2$); and others ($n = 5$)]. Finally, 40% of the patients were taking benzodiazepines (n = 52) and 6 patients took an anticholinergic agent (4.6%).

CLINICAL ASSESSMENT

All patients were assessed with the Bush–Francis Catatonia Rating Scale (BFCRS) (18), the Positive and Negative Syndrome Scale (PANSS) (19), the Young Mania Rating Scale (YMRS), and the Simpson–Angus Scale (SAS).

The BFCRS is used to recognize and score catatonic signs and symptoms. It measures the severity of 23 catatonic signs. By scoring the first 14 items of the BFCRS, the instrument can be used as a screening tool. If two or more of the BFCRS signs are present, the presence of catatonia can be considered. Items of the BFCRS are scored on a 0–3 point scale. The PANSS is a widely used medical scale for measuring symptom severity of patients with schizophrenia. Scores ranging from 1 to 7 are given on 30 different symptoms in three subscales (positive scale 7 items, negative scale 7 items, general psychopathology scale 16 items), with total score ranging from 30 to 210. In order to measure depressive symptoms we used a depression-subscale of the PANSS (PANSS-dep) including items depression, anxiety and guilt feelings. The YMRS is a rating scale to assess manic symptoms. The scale has 11 items and is based on the patient's subjective report of his or her clinical condition over the previous 48 h. Additional information is based upon clinical observations made during the course of the clinical interview. The SAS is used to measure extrapyramidal symptoms. It is composed of 10 items and signs.

RESULTS

CATATONIA SYMPTOMATOLOGY

Catatonic symptomatology was highly prevalent in our patient sample. When focusing on the first 14 items of the BFCRS, which are suggested for using the instrument as a screening tool, 101 patients (77.7%) had at least 1 symptom scoring 1 or higher, whereas 66 patients (50.8%) had at least 2 symptoms. Interestingly, when focusing on the DSM-5 criteria of catatonia (at least 3 out of 12 selected symptoms), 22 patients (16.9%) fulfill the diagnostic criteria, which still implied a high prevalence rate, but drastically lower than when using the BFCRS-criteria, and interestingly and unexpectedly, also lower than with the DSM-IV-TR criteria (see **Table 1**).

In our patient sample, the most prevalent catatonic symptoms were excitement ($n = 49$; 37.7%), perseveration ($n = 32$; 24.6%), impulsivity ($n = 31$; 23.8%), and verbigeration ($n = 31$; 23.8%), whereas, a grasp reflex or waxy flexibility could not be observed in any of the patients. Similarly, catatonic symptoms such as mitgehen ($n = 3$; 2.3%), gegenhalten ($n = 2$; 1.5%), or ambitendency ($n = 3$; 2.3%) could only seldomly be observed (see **Table 2**).

A factor analysis (Principal Component Analysis, varimax rotation) was conducted in order to generate catatonic symptom clusters. Given that items grasp reflex and waxy flexibility had a zero variance, these items were excluded from the analysis. This yielded six symptom clusters (see **Table 3**): a negative factor including immobility/stupor, mutism, staring, posturing, rigidity, negativism, withdrawal, gegenhalten, and ambitendency; a stereotypy/mannerism factor including stereotypy,

Table 1 | Prevalence of catatonia in an acute psychiatric patient sample according to different criteria.

	DSM-IV (20)	DSM-V (11)	BFCRS (18)	Fink and Taylor (21, 22)
Psychotic disorder	19 (28.4%)	14 (20.9%)	48 (71.6%)	9 (13.4%)
Mood disorder	7 (31.8%)	5 (22.7%)	17 (77.3%)	5 (22.7%)
Substance use disorder	1 (7.1%)	0 (0%)	3 (21.4%)	0 (0%)
Another diagnosis	5 (18.5%)	3 (11.1%)	14 (51.9%)	2 (7.4%)
Total patient group	32 (24.6%)	22 (16.9%)	82 (63.1%)	16 (12.3%)

Table 2 | Scores on the individual items of the BFCRS.

	Score = 0 (absent symptom)	Score = 1	Score = 2	Score = 3	Patients with symptom (*N*)
Excitement	81	35	14	0	49
Immobility/stupor	107	18	5	0	23
Mutism	117	4	6	3	13
Staring	101	22	5	2	29
Posturing/catalepsy	112	11	4	3	18
Grimacing	119	11	0	0	11
Echopraxia/echolalia	126	3	1	0	4
Stereotypy	104	19	6	1	26
Mannerisms	114	7	7	2	16
Verbigeration	99	17	12	2	31
Rigidity	115	13	2	0	15
Negativism	124	5	1	0	6
Waxy flexibility	130	0	0	0	0
Withdrawal	107	12	6	5	23
Impulsivity	99	13	18	0	31
Automatic obedience	121	4	5	0	9
Mitgehen	127	0	0	3	3
Gegenhalten	128	0	0	2	2
Ambitendency	127	0	0	3	3
Grasp reflex	130	0	0	0	0
Perseveration	98	0	0	32	32
Combativeness	112	15	2	1	18
Autonomic abnormality	116	13	1	0	14

mannerisms, and mitgehen; an echo/perseveration factor including echophenomena, verbigeration, and perseveration; an excitement factor encompassing items excitement, impulsivity, and combativeness; a grimacing factor only including that specific item, and finally, an autonomic factor including autonomic abnormalities and, strangely, automatic obedience. Composite scores based on this principal component analysis were calculated.

CLINICAL SYMPTOMATOLOGY

All patients completed the PANSS. Out of the total patient group, 88 (67.7%) had a PANSS-pos score higher than 14 reflecting a symptom state that was higher than dubious and 51 patients (39.2%) had at least mild psychotic symptomatology (i.e., a PANSS-pos score of 21 or higher). Similarly, all patients completed a YMRS: 29 patients (22.3%) had a score of 20 or higher, reflecting (hypo)manic symptomatology whereas only 34 patients (26.2%) had an absent of manic symptomatology (i.e., a maximum score of 6).

TO WHAT EXTENT IS THE CATATONIC SYMPTOMATOLOGY DETERMINED BY THE UNDERLYING DIAGNOSIS?

The total patient sample was divided in four groups: patients with a psychotic disorder ($n = 67$; 51.5%), patients with a mood disorder ($n = 22$; 16.9%; composed of 16 bipolar patients and 6 patients with a major depressive disorder), patients with a substance use disorder (SUD; $n = 14$; 10.8%), and patients with another diagnosis (patients-OD; $n = 27$; 20.8%).

Patients with a psychotic or mood disorder as a primary diagnosis had the most prominent catatonic symptom profiles (see **Figure 1**).

Compared to patients with a SUD or the patient-OD group psychotic patients tended to score higher on the stereotypy/mannerism symptom cluster (SUD: $p = 0.044$; patient-OD: $p = 0.076$), the negative symptom cluster (SUD: $p = 0.069$; patient-OD: $p = 0.121$), and on the excitement symptom cluster (SUD: $p = 0.021$; patient-OD: $p = 0.063$). No differences between the psychosis group and the combined mood disorder group could be seen. However, when only the bipolar patients entered analyses, these patients had significant more excitement symptoms ($p = 0.015$) than the patients with a psychotic illness, whereas, the latter group had significantly more excitement symptoms compared to the major depressive disorder group ($p = 0.029$). Very similar results were found after controlling for extrapyramidal symptomatology by use of the total score on the SAS. These results could mostly be explained by the fact that the SUD- and patient-OD groups hardly showed any catatonic symptomatology.

Psychotic symptomatology correlated strongly with excitement symptomatology ($r = 0.528$, $p < 0.001$) and to a lesser degree with the stereotypy/mannerisms symptom cluster ($r = 0.289$; $p = 0.001$) and the echo/perseveration symptom cluster ($r = 0.185$; $p = 0.035$). Similarly, manic symptomatology as assessed by the YMRS correlated strongly with the excitement symptom cluster ($r = 0.596$; $p < 0.001$) and to a lesser extent with the stereotypy/mannerisms symptom cluster ($r = 0.277$,

Table 3 | Factor analysis (principal component analysis), varimax rotation on the items of the BFCRS[a].

	Negative factor	Stereotypy/mannerisms factor	Echo/perseveration factor	Excitement factor	Grimacing factor	Autonomic factor
Excitement	−0,320	0,509	0,070	**0,442**	0,070	−0,156
Immobility/stupor	**0,836**	−0,06	0,096	−0,135	−0,019	−0,143
Mutism	**0,837**	0,013	−0,068	−0,069	0,047	−0,177
Staring	**0,790**	0,140	0,086	−0,111	0,055	0,105
Posturing/catalepsy	**0,900**	0,007	−0,038	−0,037	0,006	−0,094
Grimacing	−0,065	0,142	−0,046	0,180	**0,637**	−0,065
Echopraxia/echolalia	−0,092	−0,209	**0,756**	−0,066	0,204	−0,247
Stereotypy	−0,074	**0,830**	0,096	0,008	−0,026	−0,005
Mannerisms	0,139	**0,608**	−0,071	0,215	0,053	0,138
Verbigeration	0,109	0,188	0,727	0,070	−0,149	0,270
Rigidity	**0,777**	0,069	0,146	0,096	−0,034	0,183
Negativism	**0,663**	0,115	0,033	0,137	0,490	0,257
Withdrawal	**0,665**	−0,129	−0,199	0,004	−0,219	−0,103
Impulsivity	0,112	0,492	0,134	**0,399**	0,192	0,030
Automatic obedience	−0,047	0,068	0,010	0,154	−0,068	**0,714**
Mitgehen	0,075	**0,688**	−0,018	−0,403	0,270	−0,127
Gegenhalten	**0,678**	−0,016	0,164	0,280	−0,041	0,053
Ambitendency	**0,650**	0,223	0,004	−0,069	0,545	0,068
Perseveration	0,243	0,348	**0,560**	−0,036	−0,403	0,09
Combativeness	0,006	0,068	−0,050	**0,728**	0,147	−0,018
Autonomic Abnormality	−0,033	−0,109	0,042	−0,285	0,053	**0,660**

[a] *Items waxy flexibility and grasp reflex were excluded from this analysis, because of the zero variance on these items.*
Composite scores based on this principal component analysis (symptoms scores in bold) were calculated.

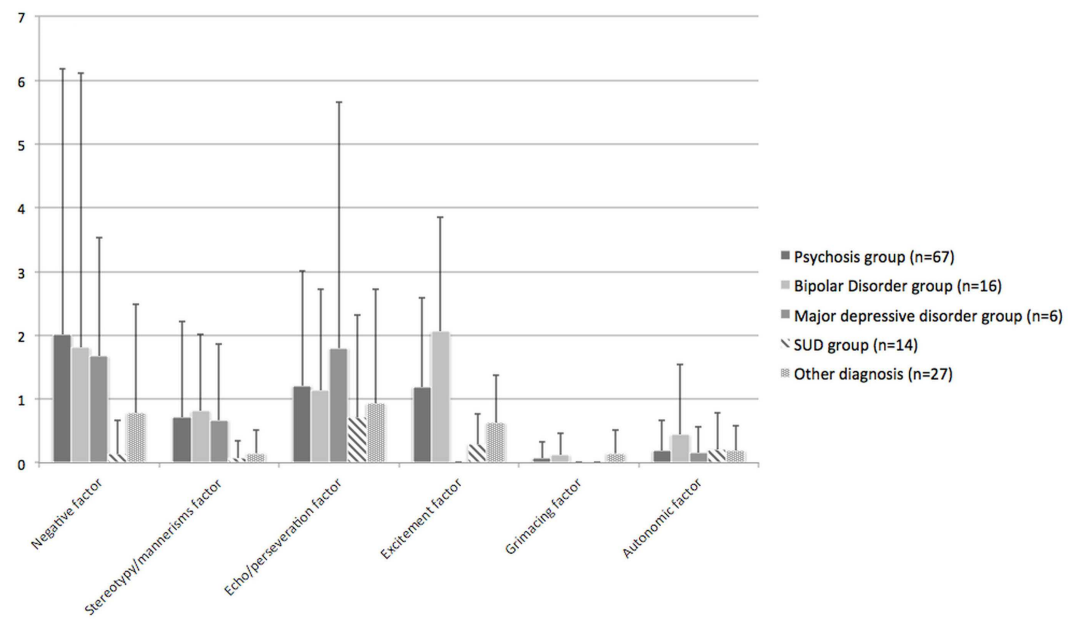


FIGURE 1 | Distribution of catatonic signs.

$p = 0.001$). It should be noted that the PANSS-pos subscale and the YMRS strongly intercorrelated ($r = 0.695$; $p < 0.011$), which undoubtedly confounded these results.

A PANSS-dep was calculated including items depression, anxiety, and guilt feelings. Kontaxakis and colleagues found this subscale to intercorrelate with the Hamilton Depression subscale (23).

PANSS-dep was inversely correlated with the grimacing factor ($r = -0.288$; $p = 0.001$) and tended toward an inversely correlation with the excitement factor ($r = -0.170$; $p = 0.054$), suggesting that depressive patients had these catatonic symptoms to a lesser degree than their non-depressed peers.

The total score on the SAS also correlated with the negative catatonia symptomatology ($r = 0.350$; $p < 0.001$) and with the echo/perseveration symptoms ($r = 0.318$; $p < 0.001$), which suggests that catatonic symptoms and extrapyramidal symptoms could not clearly be delineated from each other in our patient sample.

DISCUSSION

Out of the 130 patients that were admitted to an enclosed psychiatric ward, 101 patients (77.7%) had at least 1 symptom, whereas 66 patients (50.8%) had at least 2 symptoms when screened for catatonia symptoms, irrespective of the underlying diagnosis. In other words, catatonic symptomatology was highly prevalent in our patient population, although in most cases mildly. The most prevalent catatonic symptoms were excitement ($n = 49$; 37.7%), perseveration ($n = 32$; 24.6%), impulsivity ($n = 31$; 23.8%), and verbigeration ($n = 31$; 23.8%).

Our current findings demonstrate the presence of at least one symptom that is labeled as being catatonic by the BFCRS in most of the patients admitted to an enclosed psychiatric ward. In other studies, catatonia has been reported in 5–20% of acutely ill patients admitted to psychiatric units (9, 10, 18, 21, 24–26). In these studies, different criteria to diagnose catatonia were used, which renders a comparison between different studies on the prevalence of catatonia more difficult. For example, in the study of Lee, DSM-criteria were used to classify catatonia (24). When we used the latest DSM-criteria, only 16.9% of the patients ($n = 22$) could be considered as being catatonic. In the study of Ungvari, the diagnosis was made in the presence of four or more signs or symptoms with at least one having a score "2" or above on the BFCRS (26), which again, are more strict criteria than those used in our study. Fink and Taylor made their own diagnostic criteria with emphasis on the duration of the catatonic symptoms (22). Consequently, these divergent findings raise two interesting points. Depending on which criteria are being used, the more strict DSM-criteria versus the more liberal criteria suggested by Bush and colleagues (i.e., two items on the BFCRS), very different prevalence rates were found, which clearly emphasizes the shortcomings caused by a lack of clear-cut criteria (27). Of note, the DSM-5 criteria for catatonia appear to be even more strict than those of its predecessor, even if all 12 items, which were clustered in five categories in the DSM-IV can now be scored separately. This is mainly due to the fact that now three instead of two items have to be present. On the other hand, the high prevalence of symptoms using the BFCRS-criteria was mostly explained by the presence of mild symptomatology, whereas, more severe symptoms were present in a minority of our sample. Consequently, our results seem to point out that catatonic features, and more broadly psychomotor symptoms, may deserve a dimensional approach, much like cognitive symptoms associated with these psychiatric illnesses (27). It should also be noted that the most prevalent catatonic symptoms were not the strictly motor symptoms, which mostly seem associated with the traditional view on catatonia. Cognitive symptoms like perseveration and affective symptoms like excitement were the most prevalent and their validity and specificity as catatonic features should be questioned, especially in the more mild presentations. The unknown pathophysiology may contribute to the different views on catatonia. An unifying pathogenesis of catatonia that explains all motor, vegetative, and behavioral symptoms remains elusive. As a result, an unclear clinical concept of catatonia exists with the use of different diagnostical criteria and different rating scales to score catatonic symptomatology.

In our study, no significant differences in overall prevalence of catatonia between the psychosis group and the combined mood disorder group could be seen. Other studies also show that the syndrome is highly prevalent in both psychotic and mood disorders (17). Several studies found that the frequency of catatonia as part of schizophrenia varies with a range between 4 and 15% (5–8). Slightly higher prevalence rates have been shown in mood disorders with prevalence rates of 10–25% in bipolar disorder and up to 20% of patients with an unipolar depressive disorder (14–16, 22). However, again, different criteria for catatonia were used in these studies.

Different catatonia symptom profiles were found, depending on the underlying psychopathology. Psychotic patients tended to score higher on the stereotypy/mannerism symptom cluster, the negative symptom cluster, and the excitement symptom cluster compared to patients with a substance use disorder and patients with another diagnosis, but not compared to patients with mood disorders. In this line, psychotic symptomatology correlated strongly with excitement symptomatology and to a lesser degree with the stereotypy/mannerisms symptom cluster and the echo/perseveration symptom cluster. Similarly, manic symptomatology correlated strongly with the excitement symptom cluster and to a lesser extent with the stereotypy/mannerisms symptom cluster. Kraepelin already suggested that catatonia had a different symptomatology depending on the underlying pathology. Partly in line with our results, he described that negativism and mannerism were mainly associated to dementia praecox (4). Similarly, Schneider compared patients with catatonic (schizophrenic) and manic excitement, respectively and found that schizophrenic agitated patients displayed more blocking, waxy flexibility, stereotyped speech, mutism, and negativism (28). In a study of catatonic adolescents, automatic obedience and stereotypies were significantly more associated with schizophrenic than they were with non-schizophrenic catatonia (29). Finally, Krüger and colleagues found that catatonic chronic schizophrenia is mainly associated with catalepsy, waxy flexibility, and volitional disturbances such as automatic obedience and negativism, as well as mannerisms and abnormal involuntary movements such as grimacing, jerky movements, and stereotypies. In contrast, manic patients mainly displayed catatonic excitement, whereas, depressed patients were characterized by catatonic inhibition in terms of stupor, mutism, and rigidity (15). This was also in line with our findings, since symptoms of excitement and combativeness was significantly more present in the manic patients sample and significantly less in the depressed group, when compared to the psychotic patients sample.

Some limitations of our study should be pointed out. First, the impact of medication could be a confounding factor in our study.

A vast number of patients were taking benzodiazepines at the time of testing, which could have masked more severe presentations of the catatonic syndrome. Another limitation of the study is the lack of a depression scale. To overcome this limitation, we used the PANSS-dep but a dedicated depression scale would have been more elegant. Moreover, the sample size was rather small, especially in some subgroups. Larger scale trials are needed to replicate our findings.

In conclusion, there was a high prevalence of catatonic symptomatology. Remarkably, there is an important difference in exact prevalence depending on the criteria being used, which makes it clear that we need clear-cut criteria. Another important finding is the fact that the catatonic presentation may vary depending on the underlying pathology, although an unambiguous delineation between these catatonic presentations cannot be made. Future research is needed to determine diagnostical criteria of catatonia, which are clinically relevant.

AUTHOR CONTRIBUTION

All authors met ICMJE criteria and all those who fulfilled those criteria were listed as authors. All authors had access to the study data and made the final decision about where to present these data.

ACKNOWLEDGMENTS

The authors thank the study participants, without whom the study would never have been accomplished.

REFERENCES

1. Dhossche DM, Stoppelbein L, Rout UK. Etiopathogenesis of catatonia: generalizations and working hypotheses. *J ECT* (2010) **26**:253–8. doi:10.1097/YCT.0b013e3181fbf96d
2. Mahendra B. Where have all the catatonics gone? *Psychol Med* (1981) **11**:669–71. doi:10.1017/S0033291700041155
3. Bleuler E. *Dementia Praecox or Group of Schizophrenias* [1911]. New York, NY: International Universities Press (1950).
4. Kraepelin E. *Dementia Praecox and Paraphrenia.* Edinburgh: E&S Livingstone (1919). 331 p.
5. Deister A, Marneros A. Prognostic value of initial subtype in schizophrenic disorders. *Schizophr Res* (1994) **12**:145–57. doi:10.1016/0920-9964(94)90072-8
6. Ungvari GS, Leung SK, Ng FS, Cheung H-K, Leung T. Schizophrenia with prominent catatonic features ('catatonic schizophrenia'): I. Demographic and clinical correlates in the chronic phase. *Prog Neuropsychopharmacol Biol Psychiatry* (2005) **29**:27–38. doi:10.1016/j.pnpbp.2004.08.007
7. Beratis S, Gabriel J, Hoidas S. Age at onset in subtypes of schizophrenic disorders. *Schizophr Bull* (1994) **20**:287–96. doi:10.1093/schbul/20.2.287
8. Kleinhaus K, Harlap S, Perrin MC, Manor O, Weiser M, Harkavy-Friedman JM, et al. Catatonic schizophrenia: a cohort prospective study. *Schizophr Bull* (2012) **38**:331–7. doi:10.1093/schbul/sbq087
9. Fink M, Taylor MA. The catatonia syndrome. *Arch Gen Psychiatry* (2009) **66**:1173–7. doi:10.1001/archgenpsychiatry.2009.141
10. Van Harten PN. [Catatonia: a syndrome to be remembered]. *Tijdschr Psychiatr* (2005) **6**:371–82.
11. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition.* Washington, DC: American Psychiatric Association (2013).
12. Pommepuy N, Januel D. [Catatonia: resurgence of a concept. A review of the international literature]. *Encephale* (2002) **28**:481–92.
13. Caroff SN, Mann SC, Francis A, Fricchione GL. *Catatonia. From Psychopathology to Neurobiology.* London: American Psychiatric Publishing (2004). 248 p.
14. Bräunig P, Krüger S, Shugar G. Prevalence and clinical significance of catatonic symptoms in mania. *Compr Psychiatry* (1998) **39**:35–46. doi:10.1016/S0010-440X(98)90030-X
15. Krüger S, Bagby RM, Höffler J, Bräunig P. Factor analysis of the catatonia rating scale and catatonic symptom distribution across four diagnostic groups. *Compr Psychiatry* (2003) **44**:472–82. doi:10.1016/S0010-440X(03)00108-1
16. Starkstein SE, Petracca G, Tesón A, Chemerinski E, Merello M, Migliorelli R, et al. Catatonia in depression: prevalence, clinical correlates, and validation of a scale. *J Neurol Neurosurg Psychiatry* (1996) **60**:326–32. doi:10.1136/jnnp.60.3.326
17. Usman DM, Olubunmi OA, Taiwo O, Taiwo A, Rahman L, Oladipo A. Comparison of catatonia presentation in patients with schizophrenia and mood disorders in Lagos, Nigeria. *Iran J Psychiatry* (2011) **6**:7–11.
18. Bush G, Fink M, Petrides G, Dowling F, Francis A. Catatonia. I. Rating scale and standardized examination. *Acta Psychiatr Scand* (1996) **93**:129–36. doi:10.1111/j.1600-0447.1996.tb09814.x
19. Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophr Bull* (1987) **13**:261–76. doi:10.1093/schbul/13.2.261
20. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition.* Washington, DC: American Psychiatric Association (2000).
21. Fink M, Taylor MA. *Catatonia: A Clinician's Guide to Diagnosis and Treatment.* Cambridge: Cambridge University prEss (2003). 256 p.
22. Taylor MA, Fink M. Catatonia in psychiatric classification: a home of its own. *Am J Psychiatry* (2003) **160**:1233–41. doi:10.1176/appi.ajp.160.7.1233
23. Kontaxakis VP, Havaki-Kontaxaki BJ, Stamouli SS, Margariti MM, Collias CT, Christodoulou GN. Comparison of four scales measuring depression in schizophrenic inpatients. *Eur Psychiatry* (2000) **15**:274–7. doi:10.1016/S0924-9338(00)00232-7
24. Lee JW, Schwartz DL, Hallmayer J. Catatonia in a psychiatric intensive care facility: incidence and response to benzodiazepines. *Ann Clin Psychiatry* (2000) **12**:89–96. doi:10.3109/10401230009147094
25. Rosebush PI, Hildebrand AM, Furlong BG, Mazurek MF. Catatonic syndrome in a general psychiatric inpatient population: frequency, clinical presentation, and response to lorazepam. *J Clin Psychiatry* (1990) **51**:357–62.
26. Ungvari GS, Leung CM, Wong MK, Lau J. Benzodiazepines in the treatment of catatonic syndrome. *Acta Psychiatr Scand* (1994) **89**(4):285–8. doi:10.1111/j.1600-0447.1994.tb01515.x
27. Morrens M, Docx L, Walther S. Beyond boundaries: in search of an integrative view on motor symptoms in schizophrenia. *Front Psychiatry* (2014) **5**:145. doi:10.3389/fpsyt.2014.00145
28. Schneider K. Uber Wesen und Bedeutung katatonischer Symptome. *Zeitschrift fur die gesamte Neurol und Psychiatr* (1914) **22**:486–505. doi:10.1007/BF02869176
29. Cohen D, Nicolas JD, Flament MF, Périsse D, Dubos PF, Bonnot O, et al. Clinical relevance of chronic catatonic schizophrenia in children and adolescents: evidence from a prospective naturalistic study. *Schizophr Res* (2005) **76**:301–8. doi:10.1016/j.schres.2005.01.014

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Received: 07 October 2014; accepted: 19 November 2014; published online: 03 December 2014.
Citation: Stuivenga M and Morrens M (2014) Prevalence of the catatonic syndrome in an acute inpatient sample. Front. Psychiatry 5:174. doi: 10.3389/fpsyt.2014.00174
This article was submitted to Schizophrenia, a section of the journal Frontiers in Psychiatry.

frontiers in PSYCHIATRY

REVIEW ARTICLE
published: 09 December 2014
doi: 10.3389/fpsyt.2014.00181

A clinical review of the treatment of catatonia

Pascal Sienaert[1,2]*, Dirk M. Dhossche[3], Davy Vancampfort[4], Marc De Hert[4] and Gábor Gazdag[5,6]

[1] Department of Mood Disorders and Electroconvulsive Therapy, University Psychiatric Center, KU Leuven, Leuven, Belgium
[2] Department of Neurosciences, KU Leuven, Leuven, Belgium
[3] Department of Psychiatry, University of Mississippi Medical Center, Jackson, MS, USA
[4] University Psychiatric Center, KU Leuven, Leuven, Belgium
[5] Center for Psychiatry and Addiction Medicine, Szent István and Szent László Hospitals, Budapest, Hungary
[6] Department of Psychiatry and Psychotherapy, Faculty of Medicine, Semmelweis University, Budapest, Hungary

Edited by:
Mihaly Hajos, Yale University School of Medicine, USA

Reviewed by:
Mihaly Hajos, Yale University School of Medicine, USA
Sebastian Walther, University Hospital of Psychiatry, Switzerland
Manuel Morrens, University Antwerp, Belgium

***Correspondence:**
Pascal Sienaert, Department of Mood Disorders and Electroconvulsive Therapy, University Psychiatric Center, KU Leuven (University of Leuven), Campus Kortenberg, Leuvensesteenweg 517, Kortenberg 3070, Belgium
e-mail: pascal.sienaert@uc-kortenberg.be

Catatonia is a severe motor syndrome with an estimated prevalence among psychiatric inpatients of about 10%. At times, it is life-threatening especially in its malignant form when complicated by fever and autonomic disturbances. Catatonia can accompany many different psychiatric illnesses and somatic diseases. In order to recognize the catatonic syndrome, apart from thorough and repeated observation, a clinical examination is needed. A screening instrument, such as the Bush-Francis Catatonia Rating Scale, can guide the clinician through the neuropsychiatric examination. Although severe and life-threatening, catatonia has a good prognosis. Research on the treatment of catatonia is scarce, but there is overwhelming clinical evidence of the efficacy of benzodiazepines, such as lorazepam, and electroconvulsive therapy.

Keywords: catatonia, benzodiazepines, electroconvulsive therapy, glutamate antagonists, zolpidem, transcranial magnetic stimulation

INTRODUCTION

Catatonia is a severe motor syndrome with an estimated prevalence among psychiatric inpatients of about 10% (1, 2). Catatonia can accompany many different psychiatric illnesses and somatic diseases. A minority of catatonic patients suffers from schizophrenia (30%), while a majority has a bipolar disorder (43%) (1, 3, 4). Catatonia has also been linked to other psychiatric disorders, such as obsessive-compulsive disorder (5), post-traumatic stress disorder (6, 7), or withdrawal from alcohol (8) or benzodiazepines (9, 10). In up to 25% of cases, catatonia is related with general medical or neurologic conditions (1, 11). Recently, it was shown repeatedly that catatonic symptoms are observable in most patients diagnosed with anti-*N*-methyl-D-aspartate receptor (anti-NMDAR) encephalitis (12, 13). In adolescents and young adults with autism, catatonia is found in 12–17% (14). Pediatric catatonia also emerges in patients with tic disorders, and a variety of other (developmental) disorders (15). The same principles of evaluation and treatment seem to apply to pediatric patients as in adult patients (15, 16).

A life-threatening situation occurs when catatonia is accompanied by fever and autonomic abnormalities. Malignant catatonia, coined as "lethal catatonia" by Stauder in 1934 (17), presents as a constellation of catatonia, stuporous exhaustion, autonomic instability, respiratory failure, collapse, coma, and often death if left untreated. This clinical picture is very close to what is observed in neuroleptic malignant syndrome (NMS), which is considered by several experts to be a drug-induced form of catatonia (18).

EVALUATION, DIFFERENTIAL DIAGNOSIS, AND TREATMENT

An effective treatment starts with a swift and correct diagnosis. In any patient exhibiting marked deterioration in psychomotor function and overall responsiveness, catatonia should be considered. Moreover, any patient that is admitted to a psychiatric ward with a severe psychiatric disorder, such as depression, bipolar disorder, a psychotic disorder, or autism spectrum disorder, should be examined routinely (19). Some signs and symptoms are evident upon observation of the patient during a psychiatric interview. Other specific symptoms, however, such as automatic obedience, ambitendency, negativism should be elicited during a neuropsychiatric examination (19, 20). A rating scale can be used as a screening instrument and aid in the detection and quantification of catatonia. A number of rating scales have been found reliable, sensitive and specific: the Rogers Catatonia Scale, the Bush-Francis Catatonia Rating Scale (BFCRS) (and its revised version), the Northoff Catatonia Rating Scale, and the Braunig Catatonia Rating Scale (19). Early detection of catatonia is of great importance, since the presence of catatonic signs possesses significant prognostic and therapeutic value (19).

Unfortunately, no laboratory test specifically defines catatonia. The "diagnostic weight" of several proposed laboratory and imaging tests is limited (21). Possible laboratory tests, primarily to assess various underlying conditions, include a complete blood count and metabolic panel, erythrocyte sedimentation rate, blood urea nitrogen, creatinine, serum iron, and creatinine-phosphokinase, antinuclear antibodies, and urinalysis, and magnetic resonance imaging, electroencephalogram, cerebrospinal

fluid analysis (4, 11). Given the frequent association with anti-NMDAR-encephalitis, detection of IgG antibodies to NMDAR in cerebrospinal fluid or serum is advisable (22). Since serum iron was found to be reduced in NMS compared to catatonia (23), some authors see low serum iron as a risk factor for developing NMS after using antipsychotics in a catatonic patient (24). A drug screen to detect common illicit and prescribed substances is necessary.

PROGNOSIS

Prognosis of catatonia is good, especially with early and aggressive treatment. In mood disorders, prognosis is probably better than in psychotic disorders. Kraepelin, who classified catatonia as a type of dementia praecox, wrote, in the 9th edition of his textbook, that almost half of catatonic attacks begin with a depressive phase and that these patients had a better prognosis. Hoch, in a monograph on benign stupors, reports good outcomes ('*remission and return to the community*') in 13 patients with manic-depressive illness, and a poor outcome in 12 schizophrenics (25). In more recent studies, results are conflicting. Most of the available data confirm a worse prognosis in the context of schizophrenia. In a randomized double-blind, placebo-controlled trial in 18 patients with chronic schizophrenia, who also displayed enduring catatonic features, 6 mg lorazepam per day for 12 weeks did not have any effect on catatonic symptoms (26). In another recent study, 73% of 24 patients with catatonia remitted within 6 days after starting benzodiazepines: partial responders (6/24) all had schizophrenia (27). In a retrospective study ECT was only partially efficacious in 2 of 4 patients with schizophrenic catatonia, whereas 5 out of 5 patients with mood disorder fully recovered (28). In a small open study, however, lorazepam (4–12.5 mg/day) was reported ineffective in 5 of 20 patients; all 5 with mood disorders (29). In a recent retrospective chart study on the effects of lorazepam in 107 inpatients with a primary diagnosis of catatonia, there was no significant difference between patients with mood disorder and those with a non-affective psychotic disorder (30, 31). Similarly, in an ECT-study in 22 patients, 13 (59%) of which had a mood disorder, no statistically significant difference was found in the effectiveness of the resolution of catatonic symptoms in persons with mood disorder versus schizophrenia (32), although the authors stress that in the patients with mood disorders more catatonic symptoms resolved with ECT than in the other group.

A factor that might complicate the difference in reported response rates of affective versus schizophrenic catatonia is chronicity. At least part of the studies showing a worse response in the context of schizophrenia have included patients with chronic catatonia (4, 26, 33). Some authors have suggested that "chronic catatonia" in the context of schizophrenia is phenomenologically different and less responsive to either benzodiazepines or ECT (34), and thus carries a less favorable prognosis then the acute forms of catatonia. The fact that a longer duration of the episode has been reported to predict a worse response should not be seen as a reason to withhold adequate treatment in patients presenting with longstanding or resistant catatonic symptoms. Catatonia that is not effectively treated may persist for years, but should nevertheless be promptly treated upon detection. A number of cases are illustrative of the *overall* good prognosis, even in chronic and longstanding catatonic symptoms. A man with a 17-year history of catatonia responded swiftly to the administration of lorazepam (35); a 15-year-old girl with catatonic lupus, resistant to several treatments was successfully treated with ECT after 3 months (36). A man developing catatonia after myocardial infarction remained catatonic for 1.5 years until he was treated with ECT (37). A mentally retarded boy with catatonia of 5 year's duration improved with lorazepam (38). Both Ripley and Millson (39) and Salam et al. (40) reported positive response to lorazepam in two patients with psychogenic catatonia that lasted 2 1/2 years and 3 months, respectively. A long treatment delay should, however, be avoided since it can lead to a variety of serious medical complications, some of which may be lethal (41).

In the above mentioned retrospective lorazepam-study in 107 inpatients (30), predictors of response to lorazepam were examined. A longer illness duration, the presence of mutism, third-person auditory hallucinations and 'made phenomena' (in which the individual feels he is being made to do something) predicted a poor response, whereas the presence of waxy flexibility predicted a good response (30). It should be noted that low lorazepam doses (3–6 mg/day) were used. A longer illness duration also seemed to predict a worse outcome in the first 11 patients treated by László Meduna, who invented convulsive therapy in 1934 (42, 43). In a 1912 monograph, Urstein reports on 30 patients with catatonia, with various underlying conditions and a variable prognosis, being worse in patients with a higher number of episodes (44). Fink states that prognosis is especially favorable when the syndrome is dominated by stupor, hyperactivity, rapid, and pressured speech, and lability of mood, or if there is a previous episode with recovery, a rapid onset of the episode, and good social functioning prior to the episode (45, 46). Van Waarde and co-workers have examined predictors of response to ECT in 27 catatonic patients and found improvement to be significantly associated with younger age, and the presence of autonomic dysregulation, especially higher body temperature (47). There is anecdotal evidence that organic catatonia is less responsive, or does not respond at all, to ECT. Swartz and colleagues described four patients with a variety of neurological impairment (Alzheimer's disease, post-encephalitic mental retardation, cerebellar atrophy, epilepsy, and spinal injury). Patients showed only transient and partial improvement to ECT. The authors suggest that advanced pathological changes of the CNS might explain a diminished response and that these states require a particularly intensive treatment (48).

Raffin and coworkers (16) recently reported treatments used in 66 consecutively hospitalized children and adolescents between the ages 9–19 with catatonia. The most frequent comorbid conditions were schizophrenia ($N = 38$, 58%), pervasive developmental disorder ($N = 17$, 26%), medical conditions ($N = 16$, 24%), bipolar disorder ($N = 11$, 17%), and intellectual disability ($N = 8$, 12%). The naturalistic design of the study lists a wide range of treatments in various combinations. Average catatonia scores decreased and level of function increased during the admission. Fifty-one (77%) patients received benzodiazepines, in doses up to 15 mg of lorazepam per day, which were effective in 65% of cases. Twelve (18%) received ECT, in three cases as first-line treatment (of which two cases had malignant catatonia). One patient with schizophrenia received maintenance ECT. There was no association between sociodemographic variables, except gender (males

improved less than females) or co-morbid (medical or psychiatric) condition, and treatment response. Lower catatonia scores on admission and acute onset were associated with better clinical response. Cases with posturing and mannerisms were found to have less improvement than other cases.

TREATMENT OF CATATONIA

SUPPORTIVE MEASURES

A broad range of complications of catatonia can occur, such as aspiration pneumonia, dehydration, muscle contractures, pressure ulcers, nutritional deficiencies, severe weight loss, thiamine deficiency, electrolyte disturbances, urinary tract infections, and venous thromboembolism (11, 49, 50), some of which can lead to life-threatening situations. Some patients will require a high level of nursing care, and IV fluids and/or nasogastric tube feeds, in order to reduce the risk of morbidity and mortality caused by immobility, poor nutrition and dehydration (11). Anticoagulant therapies can be used to prevent deep vein thrombosis/pulmonary embolism in immobile patients (50). Medical complications should be treated lege artis. Given the often dramatic and prompt improvement of motor immobility after treatment, the major measure in preventing complications is a prompt diagnosis, and a rapid initiation of an adequate treatment of the catatonic state.

ANTIPSYCHOTICS

All prescribed medications should be evaluated for their potential to induce catatonic symptoms and discontinued if possible. There is some ambiguity about the role of antipsychotics but it is generally encouraged to discontinue antipsychotic treatment in patients presenting with catatonia (46). In the presence of a catatonic state, both first and second generation antipsychotics (SGA) may contribute to maintaining or worsening the catatonic state and increase the risk of developing NMS (51–54). During a prospective follow-up of 82 patients that had received antipsychotics at some point when catatonic, NMS developed in three cases (3.6%) (4), a substantially higher incidence than the estimated incidence of 0.07–1.8% in all antipsychotics-treated patients (55). The risk of worsening catatonia appears greater with neuroleptics and antipsychotics with higher D2-blockade and a higher potential of causing extrapyramidal side effects (56), but a worsening of catatonia and precipitation of NMS has also been reported in association with, e.g., olanzapine (57, 58).

Although it is generally accepted that neuroleptics are ineffective in catatonia (59), the role of the SGA in the treatment of catatonia is more ambiguous, and based on cases mostly with schizophrenia (21). SGA have weak GABA-agonist activity and 5HT2-antagonism that could stimulate dopamine release in the prefrontal cortex and thus alleviate catatonic symptoms (11). Several authors have reported a beneficial effect of SGA, such as clozapine (60–63), olanzapine (64–66), risperidone (67–70), and quetiapine (71). In one randomized controlled trial, in 14 stuporous psychotic patients, risperidone (4–6 mg/day) was compared to ECT. ECT-treated patients showed significantly greater improvement than those receiving risperidone (72).

The use of antipsychotics in the presence of catatonia should be evaluated in any individual case. We support, however, the general notion to discontinue neuroleptics because of their inefficacy and their potential of aggravating the catatonic symptoms. Once treatment with benzodiazepines or ECT is started and catatonia improves, there may be a role for SGA to target residual psychotic symptoms such as delusions or hallucinations, especially in patients with schizophrenia (69), or as a prophylactic treatment in psychotic disorders and mood disorders. SGA with low D2 blockade (quetiapine, olanzapine) or with D2 partial agonism (aripiprazole) should be favored in these situations (54).

Patients presenting with both delirium and catatonia warrant special consideration (73, 74). Catatonia is a frequent feature of delirious mania, a severe syndrome characterized by the rapid onset of delirium, mania, and psychosis. Symptoms of catatonia and delirium overlap, complicating diagnosis. Moreover, DSM states that catatonia should not be diagnosed if it occurs during the course of a delirium. The issue is important because treatments for catatonia and delirium are different, albeit with overlap. While delirium is typically treated with (typical or atypical) antipsychotics, the emergence of catatonia may caution against the use of antipsychotics (75, 76). Moreover, if catatonia is not recognized in a delirious patient, the withdrawal or withholding of benzodiazepines sometimes thought to worsen delirium may induce catatonia or leave catatonia untreated. Further studies in delirious patients are needed to aid these treatment dilemmas (77).

DIAGNOSTIC TEST

Benzodiazepines are the mainstay of the treatment of catatonia and are also helpful as a diagnostic probe. A positive *Lorazepam Challenge Test* validates the diagnosis of catatonia. After the patient is examined for signs of catatonia, 1 or 2 mg of lorazepam is administered intravenously. After 5 minutes, the patient is re-examined. If there has been no change, a second dose is given, and the patient is again reassessed (46, 78). A positive response is a marked reduction (e.g., at least 50%) of catatonic signs and symptoms, as measured with a standardized rating scale. Favorable responses usually occur within 10 min (46). If lorazepam is given intramuscularly or *per os*, the interval for the second dose should be longer: 15′ and 30′, respectively. Many clinicians will share the experience that a "lorazepam test" not only confirms the diagnosis of catatonia but that it also makes the underlying psychopathology apparent "*by permitting mute patients to speak*" (79). Analogous to the lorazepam test, a *Zolpidem Challenge Test* was proposed (80, 81). In this test 10 mg of zolpidem is administered *per os* and after 30 min the patient is examined. A positive response is a reduction of at least 50% of the BFCRS-score. After a positive response, treatment can be initiated.

BENZODIAZEPINES

Benzodiazepines are the first-choice treatment for catatonia, regardless of the underlying condition. Benzodiazepines are positive allosteric modulators of GABA-A receptors and will correct deficient GABA-ergic function in the orbitofrontal cortex (11). Following a positive *Lorazepam Challenge Test*, repeated doses of benzodiazepines can be used as a treatment. Their use is safe, easy and effective, with remission rates reported to be as high as 70–80% (4, 27, 82–87). In a naturalistic study of 66 children and adolescents with catatonia, it was found that benzodiazepines

improved catatonia in 65% of cases, that there was no relation between dose and level of improvement, that the dose was higher in some cases (up to 15 mg of lorazepam) than the dose recommended in pediatric patients, and that side effects were few (16). In a recent trial in 107 adult inpatients (49% with a psychotic disorder; 44% with a mood disorder), lower success rates were reported: two thirds responded but only one third of patients remitted (30). The authors argue that the lower remission rate could be explained by a delay between illness onset and treatment (30) but the doses used in the trial (3–6 mg per day) were inadequately low. As described above, it was shown repeatedly that chronic catatonia associated with schizophrenia is less responsive to benzodiazepines. Beckmann and colleagues, in a 5-year follow-up study, found benzodiazepines ineffective in the treatment of chronic catatonic schizophrenia (33). A comparable poor response (to lorazepam 6 mg per day) was shown in a randomized double-blind, placebo-controlled trial in 18 patients with chronic catatonia in schizophrenia (26).

Efficacy of benzodiazepines in catatonia is determined by dosage (75), and doses from 8 to 24 mg lorazepam per day are common and are tolerated without ensuing sedation, especially when instituted using daily incremental dosages (77). Most authors suggest starting at 1–2 mg of lorazepam every 4–12 h, and adjusting the dose in order to relieve catatonia without sedating the patient (11). With an adequate dose, response is usually seen within 3–7 days (75), but is some cases, response can be gradual and slow (38). If high dosages of lorazepam are used, patients should be monitored carefully for excessive sedation and respiratory compromise (77). The issue of whether some benzodiazepines are more efficacious in catatonia has not been cleared. Lorazepam is generally accepted to be a first-choice drug, demonstrating a 79% remission rate and the highest frequency of use (84). Successful use of diazepam (86–90), oxazepam (91), or clonazepam (27, 92–95) has also been reported. There is no consensus on how long benzodiazepines are to be continued, and generally they are discontinued once the underlying illness has remitted. In a number of cases, however, catatonic symptoms will emerge each time lorazepam is tapered off, urging the clinician to continue benzodiazepines for an extended period of time (96, 97).

ZOLPIDEM

Zolpidem, a positive allosteric modulator of GABA-A receptors, seems to be a safe and effective treatment alternative. To our knowledge, Mastain and colleagues were the first to report a dramatic durable improvement of catatonia, resistant to ECT and benzodiazepines, with zolpidem in a 56-year-old woman that was in a catatonic state secondary to a subcortical stroke (98). Two years later, the same group presented an open study with zolpidem in seven catatonic patients, observing remission of catatonic symptoms in five of them within 15–30 min after ingestion, lasting 2–5 h (99). They observed these therapeutic effects at a plasma concentration between 80 and 130 ng/L. They also published a case report about catatonia in a 21-year-old woman, resolving 15 min after administration of zolpidem as the plasma concentration reached a peak level of 90 ng/mL. Relapse occurred after 4 h when plasma concentrations fell below 90 ng/mL (80). In a subsequent publication of the same French group, the authors confirm a prompt response (i.e., reduction of at least 50% of symptoms) in all patients 20 min after the administration of 10 mg zolpidem, at a plasma level of 80–150 ng/L (29). These favorable results are replicated in a few case reports (100–102). In some instances, the beneficial response to zolpidem occurred after treatment with benzodiazepines and/or ECT had failed (98, 101, 102). These data have led to the proposition of a *Zolpidem Challenge Test* (see higher), and have urged some clinicians to continue treatment with zolpidem instead of benzodiazepines, using doses from 7.5 to 40 mg per day, without noticeable adverse effects. Even though the short-half life results in a transient effect on symptoms, long-term treatment with zolpidem has also been described (101, 102).

GLUTAMATE ANTAGONISTS

Because of its *N*-methyl-D-aspartic acid (NMDA) antagonist properties, amantadine (100–500 mg three times a day), and its derivative memantine (5–20 mg/day), have been tried in catatonia. Carroll and coworkers identified 25 cases of amantadine and memantine use in the treatment of catatonia (103). All cases (16/25 were psychotic disorders) were substantially improved, mostly after 1–7 days. It should be noted, however, that six of these cases were unpublished, and that seven other were cases experiencing a "*catatonia-parkinsonian syndrome*" while under treatment with the high-potency neuroleptic drugs haloperidol or fluphenazine. The symptoms diminished when neuroleptics were tapered and amantadine was added (104, 105). Since then, eleven additional cases describing the successful use of amantadine or memantine in catatonia have been published (58, 105–110). In one case, in an adolescent girl, catatonia that was resistant to ECT improved after the addition of amantadine (58). Only in a review of Hawkins and coworkers, a case is reported in which the use of amantadine remained without effect (84). It should be acknowledged, however, that negative cases are less likely to be published. Nevertheless, given these positive signals in the published literature, and evidence of its efficacy in treating the negative and cognitive symptoms of schizophrenia, amantadine should be further studied as a possible treatment option for catatonia.

OTHER AGENTS

There is anecdotal evidence from case-reports on the use of various other pharmacological agents, such as bromocriptine (111) and biperiden (112). Based on the GABA-hypothesis of catatonia, and the GABA-related working mechanism of several anti-convulsive mood stabilizers, these drugs have been proposed as a possible treatment option for the treatment of catatonia in bipolar patients. Only a few case-reports have been published. Valproate was used in several case reports (113–115), and found not only to have prophylactic effects but also "an ameliorating effect on the catatonic symptoms" (116). In a single case report, levetiracetam was advocated as a treatment for catatonia in bipolar disorder (117), given its possible mood stabilizing efficacy. It is of note, however, that levetiracetam has also been described to provoke catatonia (118). The use of topiramate (119) and carbamazepine (120) has also been reported. Although lithium has been anecdotally reported to have a beneficial effect on acute catatonic symptoms (121, 122), it is mostly described to be of use in the prevention of recurrent catatonia (121, 123–127), albeit with sometimes limited results (123).

ELECTROCONVULSIVE THERAPY

Electroconvulsive therapy should be started in a patient with catatonia that is not responding to benzodiazepines or when a decisive and rapid response is required in severe cases with life-threatening conditions such as malignant catatonia featuring high idiopathic fevers, tachycardia, severe blood pressure changes. If the underlying condition, e.g., psychotic depression, warrants ECT, this treatment may as well become the treatment of first choice.

The excellent efficacy of ECT in catatonia is generally acknowledged, even in the absence of randomized controlled evidence. The guidelines for the use of neurostimulation therapies in major depressive disorder of the Canadian Network for Mood and Anxiety Treatments define catatonia as one of the indications in which ECT should be considered as a first-line treatment (128).

Response rates in ECT are not systematically studied, but it is efficacy is described in hundreds of case reports and some small studies. In a review paper, Hawkins et al. reported an 85% (47/55) complete response rate (84). To our knowledge, only one randomized controlled ECT trial has been published. In this trial, the efficacy of ECT (BT, 3/W, $N = 8$) plus oral placebo was compared with sham ECT plus risperidone in lorazepam non-responsive non-affective catatonia. BFCRS scores reduced markedly, but the reduction was significantly more profound in the ECT group (72). Suzuki and co-workers studied both short- and long-term efficacy of ECT in intractable catatonic schizophrenia. In the acute phase, 100% of 11 patients responded to ECT. Relapse occurred in seven cases, and all occurred within 6 months. The 1-year recurrence rate was 63.6%, despite continuation pharmacotherapy (129). Relapsers received a second course of ECT followed by maintenance ECT for 1 year and four remained in remission (130). Those who relapsed again could be treated successfully with adjusting the frequency of treatment sessions (131). In another Japanese study, the efficacy of ECT was shown very clearly (132). Fifty patients presenting with catatonic symptoms, 23 of whom were diagnosed with schizophrenia, received either ECT or a benzodiazepine as first-line treatment. If benzodiazepines were ineffective, the next step was either ECT or an antipsychotic drug; if the latter failed, ECT was the last resort. Only 1 of 41 patients responded fully to benzodiazepines, and 19 responded partially. In contrast, all 17 patients who received ECT achieved remission. Payee and coworkers confirmed these favorable results: 8 of 9 (89%) lorazepam-non-responders responded to ECT (85). In another small (N = 9) prospective comparative study Escobar and colleagues (133) noted that catatonic symptoms remitted faster and to a greater extent in the depressed patients (4/9) than in those with schizophrenia (5/9).

In seven retrospective chart reviews, with a total of 222 patients, mostly benzodiazepine-non-responders, high response rates are confirmed (**Table 1**). The largest and most informative study included a chart review of 250 patients with catatonic schizophrenia, and was part of the Iowa 500 project (134). Eighty-five (40%) patients remitted (regardless of treatment used), while 53% of the 75 patients who had received ECT remitted. Another retrospective chart review was conducted in a university-affiliated inpatient unit. Seven of 19 patients presenting with catatonia were diagnosed with schizophrenia and ECT was used in four of them, experiencing partial ($N = 3$) or considerable ($N = 1$) improvement. In contrast, five out of five patients with mood disorder fully recovered after receiving ECT (28).

Rohland et al. reported ECT to be effective in 93% (26/28) of patients with catatonia admitted to an inpatient psychiatric unit (32). England et al. reported dramatic improvement in 10 of 12 (83%) patients with catatonia after 1–5 ECT sessions (63). In the largest study to date, 63 patients with catatonia (30% schizophrenia; 41% mood disorders) received bilateral ECT, thrice weekly, either as a first choice ($n = 6$), or after lorazepam had failed ($n = 57$). Fifty-six patients (89%) responded to ECT. Patients who responded in 4 sessions (31/56; 55%) had a lower duration of catatonia, a higher BFCRS-score, more often waxy flexibility and Gegenhalten, the involuntary resistance to passive movement of the extremities. Echophenomena predicted a slower response (136). The lowest response rates were reported in a retrospective study of 27 patients, treated with bitemporal ECT, often daily during the first week (47). Response rates were 59%. Probably, the smaller proportion of patients with a primary mood disorder, a significant treatment delay (a mean time interval of 2 months) may have negatively influenced treatment response. Another possible explanation is the fact that one third of the patients had been exposed to antipsychotics before ECT, which was reported earlier to be related to a decreased effectiveness (84).

The successful use of ECT in chronic catatonia has been described in a few case reports (137–140). Duration of catatonia varied from 3 months to 12 years, and in some cases protracted courses of bitemporal ECT (e.g., 17–68 treatments (138, 140) were needed to achieve a response. In several of these chronic cases, the catatonic symptoms reappeared when ECT was stopped. Some patients with chronic catatonia in schizophrenia will respond to a

Table 1 | ECT in catatonia: retrospective chart reviews.

Author(s), year	ECT EP/Schedule	Mood (%)/psychotic disorder (%)	N responders/*N* total	Responders (%)
Morrison (134)	NA/NA	0/100	40/75	53
Pataki (28)	BT/NA	56/44	6/9	67
McCall (135)	BT/NA	75/12	7/8	88
Rohland (33)	BT/3*W	59/23	26/28	93
van Waarde (47)	BT (93%)/daily [first week (56%)]	48/44	16/27	59
England (63)	BT/NA	NA	10/12	83
Raveendranathan (136)	BT/3*W	41/30	56/63	89

EP, electrode position; BT, bitemporal; N, number; NA, not available.

combination of ECT and clozapine. In a retrospective study, this combination resulted in sound clinical improvement as measured with the clinical global impression (CGI) in 22 patients (141).

A recent systematic review of treatment of (severe) autistic catatonia identified 12 cases with autism and catatonic symptoms of a few months to around 6 years' duration, treated with ECT-courses that ranged from 7 to 29 sessions. Almost all cases reported a dramatic improvement with ECT, usually after relatively few sessions. A few papers report a more mixed response to ECT. Several cases reported rapid recurrence of symptoms when ECT was discontinued or suspended (142). Consoli et al collected 59 cases of children and adolescents with catatonia treated with ECT. Response to ECT was favorable for 45 patients (76%), with partial improvement noted in 3 (5%) and a lack of response in only one (143).

Recently, several authors report on the successful use of unilateral ECT in a total number of 21 cases (36, 144), 15 of which were treated with an ultra-brief pulse (UB) width (139, 145, 146). In a case-series of 5 patients with catatonia, resistant to benzodiazepines, 4 patients experienced a full response with unilateral ECT; one patient achieved only partial response, and was switched to bitemporal without experiencing any additional benefit (144). In the largest case-series to date, of 13 catatonic patients treated, 11 had rapid symptom resolution with UB right-unilateral (RUL) ECT with minimal adverse effects. Two patients who did not improve with RUL ECT were switched to bilateral ECT, which provided no additional symptom benefit (146). These favorable results probably reflect the high responsiveness of catatonia to ECT, whatever technique is used. Most authors, however, strongly recommend bilateral ECT at substantially suprathreshold stimulus dosing in severely ill patients, arguing that there is substantially more evidence, and that transient cognitive impairment is a secondary consideration in patients with severe catatonia (41, 147).

It is generally advised to stop psychopharmacological agents prior to initiation of ECT. When there was a partial response with benzodiazepine treatment, it might be unwise to abruptly discontinue this treatment, because of possible interference with seizure threshold and the risk of aggravating the catatonic state. Lorazepam and ECT can be given concurrently. If lorazepam interferes with eliciting seizures, flumazenil, a partial benzodiazepine antagonist, can be given just before the anesthetic (75).

The number of treatments, before substantial and sustained improvement becomes obvious, cannot be predicted. Often, a rapid response is seen, after one or a few treatment sessions (63, 136), but sometimes catatonia seems to require more treatments than is necessary for the relief of major depression (138, 140). Therefore, ECT treatment must be individually tailored. In severe or malignant catatonia, daily ("en bloc") treatments for three to 5 days may be necessary. Maintenance-ECT may be useful for sustained symptom-remission.

TRANSCRANIAL MAGNETIC STIMULATION

The successful use of rTMS was reported in four cases, after 7–10 high-frequency stimulation sessions of the dorso-lateral prefrontal cortex (148–151). In one case, a 45-year-old man with schizophrenia, previously recovering from catatonia with ECT failed to improve with rTMS (152).

CONCLUSION

Catatonia is a severe psychomotor syndrome with an excellent prognosis if recognized and treated appropriately. The treatment of catatonia in children and adolescents should follow the same principles as in adults. Great care should be taken to avoid (medical) complications. Although a number of pharmacological agents have been tried successfully in catatonia, rarely, if ever, the effect is as immediate and dramatic as seen with benzodiazepines. If lorazepam is not available, zolpidem can be used as a diagnostic probe, and probably as a treatment alternative. If benzodiazepines fail (inadequate or transient response, excessive sedation), ECT should be started without delay. If the underlying condition warrants ECT-treatment, or in life-threatening situations like malignant catatonia or NMS, ECT is the treatment of first choice. It is advised to choose the most efficacious technique, i.e., bilateral standard-pulse ECT with a stimulus dose that is substantially above the seizure threshold.

REFERENCES

1. Pommepuy N, Januel D. [Catatonia: resurgence of a concept. A review of the international literature]. *Encephale* (2002) **28**(6 Pt 1):481–92.
2. Francis A, Fink M, Appiani F, Bertelsen A, Bolwig TG, Braunig P, et al. Catatonia in diagnostic and statistical manual of mental disorders, fifth edition. *J ECT* (2010) **26**(4):246–7. doi:10.1097/YCT.0b013e3181fe28bd
3. Abrams R, Taylor MA. Catatonia: a prospective clinical study. *Arch Gen Psychiatry* (1976) **33**(5):579–81. doi:10.1001/archpsyc.1976.01770050043006
4. Rosebush PI, Mazurek MF. Catatonia and its treatment. *Schizophr Bull* (2010) **36**(2):239–42. doi:10.1093/schbul/sbp141
5. Fontenelle LF, Lauterbach EC, Telles LL, Versiani M, Porto FH, Mendlowicz MV. Catatonia in obsessive-compulsive disorder: etiopathogenesis, differential diagnosis, and clinical management. *Cogn Behav Neurol* (2007) **20**(1):21–4. doi:10.1097/WNN.0b013e31802e3bc6
6. Shiloh R, Schwartz B, Weizman A, Radwan M. Catatonia as an unusual presentation of posttraumatic stress disorder. *Psychopathology* (1995) **28**(6):285–90. doi:10.1159/000284940
7. Moskowitz AK. "Scared stiff": catatonia as an evolutionary-based fear response. *Psychol Rev* (2004) **111**(4):984–1002. doi:10.1037/0033-295X.111.3.808
8. Geoffroy PA, Rolland B, Cottencin O. Catatonia and alcohol withdrawal: a complex and underestimated syndrome. *Alcohol Alcohol* (2012) **47**(3):288–90. doi:10.1093/alcalc/agr170
9. Parameswaran R, Moore K, Hannan T, Austin M. Catatonia associated with temazepam withdrawal. *Aust N Z J Psychiatry* (2011) **45**(11):1006–7. doi:10.3109/00048674.2011.607131
10. Sivakumar T, Yadav A, Sood M, Khandelwal SK. Lorazepam withdrawal catatonia: a case report. *Asian J Psychiatr* (2013) **6**(6):620–1. doi:10.1016/j.ajp.2013.05.008
11. Daniels J. Catatonia: clinical aspects and neurobiological correlates. *J Neuropsychiatry Clin Neurosci* (2009) **21**(4):371–80. doi:10.1176/appi.neuropsych.21.4.371
12. Dalmau J, Gleichman AJ, Hughes EG, Rossi JE, Peng X, Lai M, et al. Anti-NMDA-receptor encephalitis: case series and analysis of the effects of antibodies. *Lancet Neurol* (2008) **7**(12):1091–8. doi:10.1016/S1474-4422(08)70224-2
13. Gulyayeva NA, Massie MJ, Duhamel KN. Anti-NMDA receptor encephalitis: psychiatric presentation and diagnostic challenges from psychosomatic medicine perspective. *Palliat Support Care* (2014) **12**(2):159–63. doi:10.1017/S1478951513000515
14. Wing L, Shah A. Catatonia in autistic spectrum disorders. *Br J Psychiatry* (2000) **176**:357–62. doi:10.1192/bjp.176.4.357
15. Dhossche D, Goetz M, Gazdag G, Sienaert P. New DSM-5 category 'unspecified catatonia' is a boost for pediatric catatonia: review and case reports. *Neuropsychiatry* (2013) **3**(4):401–10. doi:10.2217/npy.13.42
16. Raffin M, Zugaj-Bensaou L, Bodeau N, Milhiet V, Laurent C, Cohen D, et al. Treatment use in a prospective naturalistic cohort of children and adolescents with catatonia. *Eur Child Adolesc Psychiatry* (2014). doi:10.1007/s00787-014-0595-y

17. Stauder KH. Die todliche Katatonie. *Arch Psychiatr Nervenkr* (1934) **102**:614–34. doi:10.1007/BF01813829
18. Sienaert P, Dhossche DM, Gazdag G. Adult catatonia: etiopathogenesis, diagnosis and treatment. *Neuropsychiatry* (2013) **3**(4):391–9. doi:10.2217/npy.13.41
19. Sienaert P, Rooseleer J, De Fruyt J. Measuring catatonia: a systematic review of rating scales. *J Affect Disord* (2011) **135**(1–3):1–9. doi:10.1016/j.jad.2011.02.012
20. Rooseleer J, Willaert A, Sienaert P. [Rating scales for assessing catatonia; which ones are the best?]. *Tijdschr Psychiatr* (2011) **53**(5):287–98.
21. Gazdag G, Sienaert P. Diagnosing and treating catatonia: an update. *Curr Psychiatry Rev* (2013) **9**(2):130–5. doi:10.2174/1573400511309020007
22. Lazar-Molnar E, Tebo AE. Autoimmune NMDA receptor encephalitis. *Clin Chim Acta* (2014) **438C**:90–7. doi:10.1016/j.cca.2014.08.010
23. Rosebush PI, Mazurek MF. Serum iron and neuroleptic malignant syndrome. *Lancet* (1991) **338**(8760):149–51. doi:10.1016/0140-6736(91)90138-F
24. Lee JW. Serum iron in catatonia and neuroleptic malignant syndrome. *Biol Psychiatry* (1998) **44**(6):499–507. doi:10.1016/S0006-3223(98)00109-7 Epub 1998/10/20.,
25. Hoch A, MacCurdy JT. *Benign Stupors; A Study of a New Manic-Depressive Reaction Type*. New York, NY: The Macmillan Company (1921). 284 p.
26. Ungvari GS, Chiu HF, Chow LY, Lau BS, Tang WK. Lorazepam for chronic catatonia: a randomized, double-blind, placebo-controlled cross-over study. *Psychopharmacology (Berl)* (1999) **142**(4):393–8. doi:10.1007/s002130050904
27. Lee JW, Schwartz DL, Hallmayer J. Catatonia in a psychiatric intensive care facility: incidence and response to benzodiazepines. *Ann Clin Psychiatry* (2000) **12**(2):89–96. doi:10.3109/10401230009147094
28. Pataki J, Zervas IM, Jandorf L. Catatonia in a university inpatient service (1985-1990). *Convuls Ther* (1992) **8**(3):163–73.
29. Thomas P, Cottencin O, Rascle C, Vaiva G, Goudemand M, Bieder J. Catatonia in French psychiatry: implications for the Zolpidem challenge test. *Psychiatr Ann* (2007) **37**(1):45–54.
30. Tibrewal P, Narayanaswamy J, Zutshi A, Srinivasaraju R, Math SB. Response rate of lorazepam in catatonia: a developing country's perspective. *Prog Neuropsychopharmacol Biol Psychiatry* (2010) **34**(8):1520–2. doi:10.1016/j.pnpbp.2010.08.017
31. Narayanaswamy JC, Tibrewal P, Zutshi A, Srinivasaraju R, Math SB. Clinical predictors of response to treatment in catatonia. *Gen Hosp Psychiatry* (2012) **34**(3):312–6. doi:10.1016/j.genhosppsych.2012.01.011
32. Rohland BM, Carroll BT, Jacoby RG. ECT in the treatment of the catatonic syndrome. *J Affect Disord* (1993) **29**(4):255–61. doi:10.1016/0165-0327(93)90015-C
33. Beckmann H, Fritze J, Franzek E. The influence of neuroleptics on specific syndromes and symptoms in schizophrenics with unfavourable long-term course. A 5-year follow-up study of 50 chronic schizophrenics. *Neuropsychobiology* (1992) **26**(1–2):50–8. doi:10.1159/000118896
34. Ungvari GS, Caroff SN, Gerevich J. The catatonia conundrum: evidence of psychomotor phenomena as a symptom dimension in psychotic disorders. *Schizophr Bull* (2010) **36**(2):231–8. doi:10.1093/schbul/sbp105
35. Singh LK, Praharaj SK. Immediate response to lorazepam in a patient with 17 years of chronic catatonia. *J Neuropsychiatry Clin Neurosci* (2013) **25**(3):E47–8. doi:10.1176/appi.neuropsych.12070181
36. Mon T, L'Ecuyer S, Farber NB, White AJ, Baszis KW, Hearn JK, et al. The use of electroconvulsive therapy in a patient with juvenile systemic lupus erythematosus and catatonia. *Lupus* (2012) **21**(14):1575–81. doi:10.1177/0961203312464803
37. Bulbul F, Unal A, Copoglu US, Alpak G, Savas HA. Persistent catatonia for 1.5 years finally resolved with electroconvulsive therapy. *J ECT* (2013) **29**(1):e1. doi:10.1097/YCT.0b013e318257c8fe
38. Gaind GS, Rosebush PI, Mazurek MF. Lorazepam treatment of acute and chronic catatonia in two mentally retarded brothers. *J Clin Psychiatry* (1994) **55**(1):20–3.
39. Ripley TL, Millson RC. Psychogenic catatonia treated with lorazepam. *Am J Psychiatry* (1988) **145**(6):764–5.
40. Salam SA, Pillai AK, Beresford TP. Lorazepam for psychogenic catatonia. *Am J Psychiatry* (1987) **144**(8):1082–3.
41. Nazarian RS, Liebman LS, Kellner CH. Electroconvulsive therapy (ECT) for catatonia: delay may be risky. *Lupus* (2013) **22**(3):336. doi:10.1177/0961203313476362
42. Meduna L. *Die Konvulsionstherapie der Schizophrenie*. Halle: Carl Marhold Verlagsbuch-Handlung (1937).
43. Gazdag G, Bitter I, Ungvari GS, Baran B, Fink M. Laszlo Meduna's pilot studies with camphor inductions of seizures: the first 11 patients. *J ECT* (2009) **25**(1):3–11. doi:10.1097/YCT.0b013e31819359fc
44. Urstein M. *Manisch-depressives und periodisches Irresein als Erscheinungsform der Katatonie*. Berlin: Urban und Schwarzenberg (1912).
45. Fink M. Catatonia: syndrome or schizophrenia subtype? Recognition and treatment. *J Neural Transm* (2001) **108**(6):637–44. doi:10.1007/s007020170041
46. Fink M, Taylor MA. *Catatonia: A Clinician's Guide to Diagnosis and Treatment*. New York, NY: Cambridge University Press (2003). 256 p.
47. van Waarde JA, Tuerlings JH, Verwey B, van der Mast RC. Electroconvulsive therapy for catatonia: treatment characteristics and outcomes in 27 patients. *J ECT* (2010) **26**(4):248–52. doi:10.1097/YCT.0b013e3181c18a13
48. Swartz CM, Acosta D, Bashir A. Diminished ECT response in catatonia due to chronic neurologic condition. *J ECT* (2003) **19**(2):110–4. doi:10.1097/00124509-200306000-00010
49. Rosebush PI. Perspectives on catatonia: 2 decades of personal clinical experience. *10th World Congress of Biological Psychiatry*. Prague: (2011).
50. Clinebell K, Azzam PN, Gopalan P, Haskett R. Guidelines for preventing common medical complications of catatonia: case report and literature review. *J Clin Psychiatry* (2014) **75**(6):644–51. doi:10.4088/JCP.13r08870
51. White DA, Robins AH. Catatonia: harbinger of the neuroleptic malignant syndrome. *Br J Psychiatry* (1991) **158**:419–21. doi:10.1192/bjp.158.3.419
52. White DA. Catatonia and the neuroleptic malignant syndrome – a single entity? *Br J Psychiatry* (1992) **161**:558–60. doi:10.1192/bjp.161.4.558
53. Braunig P, Kruger S, Hoffler J. [Exacerbation of catatonic symptoms in neuroleptic therapy]. *Nervenarzt* (1995) **66**(5):379–82.
54. Carroll BT, Lee JWY, Appiani F, Thomas C. The pharmacotherapy of catatonia. *Prim psychiatry* (2010) **17**(4):41–7. doi:10.1097/YCT.0b013e3181fe28bd
55. Adityanjee, Aderibigbe YA, Mathews T. Epidemiology of neuroleptic malignant syndrome. *Clin Neuropharmacol* (1999) **22**(3):151–8.
56. Lee JW. Neuroleptic-induced catatonia: clinical presentation, response to benzodiazepines, and relationship to neuroleptic malignant syndrome. *J Clin Psychopharmacol* (2010) **30**(1):3–10. doi:10.1097/JCP.0b013e3181c9bfe6
57. Lewis AL, Pelic C, Kahn DA. Malignant catatonia in a patient with bipolar disorder, B12 deficiency, and neuroleptic malignant syndrome: one cause or three? *J Psychiatr Pract* (2009) **15**(5):415–22. doi:10.1097/01.pra.0000361282.95962.9f
58. Goetz M, Kitzlerova E, Hrdlicka M, Dhossche D. Combined use of electroconvulsive therapy and amantadine in adolescent catatonia precipitated by cyber-bullying. *J Child Adolesc Psychopharmacol* (2013) **23**(3):228–31. doi:10.1089/cap.2012.0045
59. Ungvari GS, Kau LS, Wai-Kwong T, Shing NF. The pharmacological treatment of catatonia: an overview. *Eur Arch Psychiatry Clin Neurosci* (2001) **251**(Suppl 1):I31–4. doi:10.1007/PL00014198
60. Naber D, Holzbach R, Perro C, Hippius H. Clinical management of clozapine patients in relation to efficacy and side-effects. *Br J Psychiatry Suppl* (1992) **161**(17):54–9.
61. Rommel O, Tegenthoff M, Widdig W, Braunig P, Malin JP. Organic catatonia following frontal lobe injury: response to clozapine. *J Neuropsychiatry Clin Neurosci* (1998) **10**(2):237–8.
62. Hung YY, Yang PS, Huang TL. Clozapine in schizophrenia patients with recurrent catatonia: report of two cases. *Psychiatry Clin Neurosci* (2006) **60**(2):256–8. doi:10.1111/j.1440-1819.2006.01495.x
63. England ML, Ongur D, Konopaske GT, Karmacharya R. Catatonia in psychotic patients: clinical features and treatment response. *J Neuropsychiatry Clin Neurosci* (2011) **23**(2):223–6. doi:10.1176/appi.neuropsych.23.2.223
64. Cassidy EM, O'Brien M, Osman MF, Finucane J, O'Keane V. Lethal catatonia responding to high-dose olanzapine therapy. *J Psychopharmacol* (2001) **15**(4):302–4. doi:10.1177/026988110101500412
65. Martenyi F, Metcalfe S, Schausberger B, Dossenbach MR. An efficacy analysis of olanzapine treatment data in schizophrenia patients with catatonic signs and symptoms. *J Clin Psychiatry* (2001) **62**(Suppl 2):25–7.
66. Numata S, Kato O, Misawa H. Treatment of catatonia with olanzapine. *German J Psychiatr* (2002) **5**:115–6.
67. Kopala LC, Caudle C. Acute and longer-term effects of risperidone in a case of first-episode catatonic schizophrenia. *J Psychopharmacol* (1998) **12**(3):314–7. doi:10.1177/026988119801200312

68. Valevski A, Loebl T, Keren T, Bodinger L, Weizman A. Response of catatonia to risperidone: two case reports. *Clin Neuropharmacol* (2001) **24**(4):228–31. doi:10.1097/00002826-200107000-00006
69. Van Den Eede F, Van Hecke J, Van Dalfsen A, Van den Bossche B, Cosyns P, Sabbe BG. The use of atypical antipsychotics in the treatment of catatonia. *Eur Psychiatry* (2005) **20**(5–6):422–9. doi:10.1016/j.eurpsy.2005.03.012
70. Grenier E, Ryan M, Ko E, Fajardo K, John V. Risperidone and lorazepam concomitant use in clonazepam refractory catatonia: a case report. *J Nerv Ment Dis* (2011) **199**(12):987–8. doi:10.1097/NMD.0b013e3182392d7e
71. Yoshimura B, Hirota T, Takaki M, Kishi Y. Is quetiapine suitable for treatment of acute schizophrenia with catatonic stupor? A case series of 39 patients. *Neuropsychiatr Dis Treat* (2013) **9**:1565–71. doi:10.2147/NDT.S52311
72. Girish K, Gill NS. Electroconvulsive therapy in lorazepam non-responsive catatonia. *Indian J Psychiatry* (2003) **45**(1):21–5.
73. Detweiler MB, Mehra A, Rowell T, Kim KY, Bader G. Delirious mania and malignant catatonia: a report of 3 cases and review. *Psychiatr Q* (2009) **80**(1):23–40. doi:10.1007/s11126-009-9091-9
74. Lee BS, Huang SS, Hsu WY, Chiu NY. Clinical features of delirious mania: a series of five cases and a brief literature review. *BMC Psychiatry* (2012) **12**:65. doi:10.1186/1471-244X-12-65
75. Fink M, Taylor MA. Neuroleptic malignant syndrome is malignant catatonia, warranting treatments efficacious for catatonia. *Prog Neuropsychopharmacol Biol Psychiatry* (2006) **30**(6):1182–3. doi:10.1016/j.pnpbp.2006.03.029
76. Seitz DP, Gill SS. Neuroleptic malignant syndrome complicating antipsychotic treatment of delirium or agitation in medical and surgical patients: case reports and a review of the literature. *Psychosomatics* (2009) **50**(1):8–15. doi:10.1176/appi.psy.50.1.8
77. Dhossche DM, Wachtel LE, Goetz M, Sienaert P. Catatonia in psychiatric illnessess. In: Fatemi H, Clayton P, editors. *The Medical Basis of Psychiatry*. New York: Springer (2014).
78. Bush G, Fink M, Petrides G, Dowling F, Francis A. Catatonia. II. Treatment with lorazepam and electroconvulsive therapy. *Acta Psychiatr Scand* (1996) **93**(2):137–43. doi:10.1111/j.1600-0447.1996.tb09815.x
79. McEvoy JP. Relief from catatonic immobility can be maintained. *J Clin Psychopharmacol* (1986) **6**(2):126–7. doi:10.1097/00004714-198604000-00025
80. Thomas P, Rascle C, Mastain B, Maron M, Vaiva G. Test for catatonia with zolpidem. *Lancet* (1997) **349**(9053):702. doi:10.1016/S0140-6736(05)60139-0
81. Cottencin O, Warembourg F, de Chouly de Lenclave MB, Lucas B, Vaiva G, Goudemand M, et al. Catatonia and consultation-liaison psychiatry study of 12 cases. *Prog Neuropsychopharmacol Biol Psychiatry* (2007) **31**(6):1170–6. doi:10.1016/j.pnpbp.2007.04.006
82. Rosebush PI, Hildebrand AM, Furlong BG, Mazurek MF. Catatonic syndrome in a general psychiatric inpatient population: frequency, clinical presentation, and response to lorazepam. *J Clin Psychiatry* (1990) **51**(9):357–62.
83. Rosebush PI, Hildebrand AM, Mazurek MF. The treatment of catatonia: benzodiazepines of ECT? *Am J Psychiatry* (1992) **149**(9):1279–80.
84. Hawkins JM, Archer KJ, Strakowski SM, Keck PE. Somatic treatment of catatonia. *Int J Psychiatry Med* (1995) **25**(4):345–69. doi:10.2190/X0FF-VU7G-QQP7-L5V7
85. Payee H, Chandrasekaran R, Raju GV. Catatonic syndrome: treatment response to Lorazepam. *Indian J Psychiatry* (1999) **41**(1):49–53.
86. Hung YY, Huang TL. Lorazepam and diazepam rapidly relieve catatonic features in major depression. *Clin Neuropharmacol* (2006) **29**(3):144–7. doi:10.1097/01.WNF.0000221908.56361.C7
87. Huang YC, Lin CC, Hung YY, Huang TL. Rapid relief of catatonia in mood disorder by lorazepam and diazepam. *Biomed J* (2013) **36**(1):35–9. doi:10.4103/2319-4170.107162
88. McEvoy JP, Lohr JB. Diazepam for catatonia. *Am J Psychiatry* (1984) **141**(2):284–5.
89. Huang TL. Lorazepam and diazepam rapidly relieve catatonic signs in patients with schizophrenia. *Psychiatry Clin Neurosci* (2005) **59**(1):52–5. doi:10.1111/j.1440-1819.2005.01331.x
90. Hung YY, Huang TL. Lorazepam and diazepam for relieving catatonic features in multiple sclerosis. *Prog Neuropsychopharmacol Biol Psychiatry* (2007) **31**(7):1537–8. doi:10.1016/j.pnpbp.2007.06.016
91. Schmider J, Standhart H, Deuschle M, Drancoli J, Heuser I. A double-blind comparison of lorazepam and oxazepam in psychomotor retardation and mutism. *Biol Psychiatry* (1999) **46**(3):437–41. doi:10.1016/S0006-3223(98)00312-6
92. Clothier JL, Pazzaglia P, Freeman TW. Evaluation and treatment of catatonia. *Am J Psychiatry* (1989) **146**(4):553–4.
93. Martenyi F, Harangozo J, Mod L. Clonazepam for the treatment of stupor in catatonic schizophrenia. *Am J Psychiatry* (1989) **146**(9):1230.
94. Benazzi F. Parenteral clonazepam for catatonia. *Can J Psychiatry* (1991) **36**(4):312.
95. Kumar R. Acute severe catatonia in a young woman with chronic schizophrenia responding to parenteral clonazepam. *Aust N Z J Psychiatry* (2001) **35**(3):391. doi:10.1046/j.1440-1614.2001.0905i.x
96. Manjunatha N, Saddichha S, Khess CR. Idiopathic recurrent catatonia needs maintenance lorazepam: case report and review. *Aust N Z J Psychiatry* (2007) **41**(7):625–7. doi:10.1080/00048670701400032
97. Grover S, Aggarwal M. Long-term maintenance lorazepam for catatonia: a case report. *Gen Hosp Psychiatry* (2011) **33**(1):e1–3. doi:10.1016/j.genhosppsych.2010.06.006
98. Mastain B, Vaiva G, Guerouaou D, Pommery J, Thomas P. [Favourable effect of zolpidem on catatonia]. *Rev Neurol (Paris)* (1995) **151**(1):52–6.
99. Rascle C, Thomas P, Maron M, Mastain B, Guesdon I, Cottencin O, et al. Catatonia relief with zolpidem: an open study. *Eur Neuropsychopharmacol* (1997) **7**(Suppl 2):S277. doi:10.1016/S0924-977X(97)88920-1
100. Zaw ZF, Bates GD. Replication of zolpidem test for catatonia in an adolescent. *Lancet* (1997) **349**(9069):1914. doi:10.1016/S0140-6736(05)63915-3
101. Peglow S, Prem V, McDaniel W. Treatment of catatonia with zolpidem. *J Neuropsychiatry Clin Neurosci* (2013) **25**(3):E13. doi:10.1176/appi.neuropsych.11120367
102. Hlal H, Kettani N, Berhili N, Rammouz I, Aalouane R. Place du zolpidem dans le traitement des catatonies résistantes aux benzodiazépines. À propos d'un cas. *Presse Med* (2014) **43**(9):1018–20. doi:10.1016/j.lpm.2013.11.023
103. Carroll BT, Goforth HW, Thomas C, Ahuja N, McDaniel WW, Kraus MF, et al. Review of adjunctive glutamate antagonist therapy in the treatment of catatonic syndromes. *J Neuropsychiatry Clin Neurosci* (2007) **19**(4):406–12. doi:10.1176/appi.neuropsych.19.4.406
104. Gelenberg AJ, Mandel MR. Catatonic reactions to high-potency neuroleptic drugs. *Arch Gen Psychiatry* (1977) **34**(8):947–50. doi:10.1001/archpsyc.1977.01770200085010
105. Obregon DF, Velasco RM, Wuerz TP, Catalano MC, Catalano G, Kahn D. Memantine and catatonia: a case report and literature review. *J Psychiatr Pract* (2011) **17**(4):292–9. doi:10.1097/01.pra.0000400268.60537.5e
106. Babington PW, Spiegel DR. Treatment of catatonia with olanzapine and amantadine. *Psychosomatics* (2007) **48**(6):534–6. doi:10.1176/appi.psy.48.6.534
107. Muneoka K, Shirayama Y, Kon K, Kawabe M, Goto M, Kimura S. Improvement of mutism in a catatonic schizophrenia case by add-on treatment with amantadine. *Pharmacopsychiatry* (2010) **43**(4):151–2. doi:10.1055/s-0029-1242821
108. Hervey WM, Stewart JT, Catalano G. Treatment of catatonia with amantadine. *Clin Neuropharmacol* (2012) **35**(2):86–7. doi:10.1097/WNF.0b013e318246ad34
109. de Lucena DF, Pinto JP, Hallak JE, Crippa JA, Gama CS. Short-term treatment of catatonia with amantadine in schizophrenia and schizoaffective disorder. *J Clin Psychopharmacol* (2012) **32**(4):569–72. doi:10.1097/JCP.0b013e31825ebf6e
110. Ene-Stroescu V, Nguyen T, Waiblinger BE. Excellent response to amantadine in a patient with bipolar disorder and catatonia. *J Neuropsychiatry Clin Neurosci* (2014) **26**(1):E43. doi:10.1176/appi.neuropsych.13020038
111. Mahmood T. Bromocriptine in catatonic stupor. *Br J Psychiatry* (1991) **158**:437–8. doi:10.1192/bjp.158.3.437
112. Franz M, Gallhofer B, Kanzow WT. Treatment of catatonia with intravenous biperidene. *Br J Psychiatry* (1994) **164**(6):847–8. doi:10.1192/bjp.164.6.847b
113. DelBello MP, Foster KD, Strakowski SM. Case report: treatment of catatonia in an adolescent male. *J Adolesc Health* (2000) **27**(1):69–71. doi:10.1016/S1054-139X(00)00109-9
114. Kruger S, Braunig P. Intravenous valproic acid in the treatment of severe catatonia. *J Neuropsychiatry Clin Neurosci* (2001) **13**(2):303–4. doi:10.1176/appi.neuropsych.13.2.303
115. Bowers R, Ajit SS. Is there a role for valproic acid in the treatment of catatonia? *J Neuropsychiatry Clin Neurosci* (2007) **19**(2):197–8. doi:10.1176/appi.neuropsych.19.2.197

116. Yoshida I, Monji A, Hashioka S, Ito M, Kanba S. Prophylactic effect of valproate in the treatment for siblings with catatonia: a case report. *J Clin Psychopharmacol* (2005) **25**(5):504–5. doi:10.1097/01.jcp.0000177850.23534.69
117. Muneer A. Catatonia in a patient with bipolar disorder type I. *J Neurosci Rural Pract* (2014) **5**(3):314–6. doi:10.4103/0976-3147.133652
118. Chouinard MJ, Nguyen DK, Clement JF, Bruneau MA. Catatonia induced by levetiracetam. *Epilepsy Behav* (2006) **8**(1):303–7. doi:10.1016/j.yebeh.2005.04.016
119. McDaniel WW, Spiegel DR, Sahota AK. Topiramate effect in catatonia: a case series. *J Neuropsychiatry Clin Neurosci* (2006) **18**(2):234–8. doi:10.1176/appi.neuropsych.18.2.234
120. Rankel HW, Rankel LE. Carbamazepine in the treatment of catatonia. *Am J Psychiatry* (1988) **145**(3):361–2.
121. Wald D, Lerner J. Lithium in the treatment of periodic catatonia: a case report. *Am J Psychiatry* (1978) **135**(6):751–2.
122. Pheterson AD, Estroff TW, Sweeney DR. Severe prolonged catatonia with associated flushing reaction responsive to lithium carbonate. *J Am Acad Child Psychiatry* (1985) **24**(2):235–7. doi:10.1016/S0002-7138(09)60454-4
123. Gjessing LR. Lithium citrate loading of a patient with periodic catatonia. *Acta Psychiatr Scand* (1967) **43**(4):372–5. doi:10.1111/j.1600-0447.1967.tb05774.x
124. Petursson H. Lithium treatment of a patient with periodic catatonia. *Acta Psychiatr Scand* (1976) **54**(4):248–53. doi:10.1111/j.1600-0447.1976.tb00118.x
125. Looper KJ, Milroy TM. Catatonia 20 years later. *Am J Psychiatry* (1997) **154**(6):883.
126. Sugahara Y, Tsukamoto H, Sasaki T. Lithium carbonate in prophylaxis of reappearing catatonic stupor: case report. *Psychiatry Clin Neurosci* (2000) **54**(5):607–9. doi:10.1046/j.1440-1819.2000.00762.x
127. Padhy SK, Subodh B, Bharadwaj R, Arun Kumar K, Kumar S, Srivastava M. Recurrent catatonia treated with lithium and carbamazepine: a series of 2 cases. *Prim Care Companion CNS Disord* (2011) **13**(1). doi:10.4088/PCC.10l00992
128. Kennedy SH, Milev R, Giacobbe P, Ramasubbu R, Lam RW, Parikh SV, et al. Canadian network for mood and anxiety treatments (CANMAT) clinical guidelines for the management of major depressive disorder in adults. iv. neurostimulation therapies. *J Affect Disord* (2009) **117**(Suppl 1):S44–53. doi:10.1016/j.jad.2009.06.039
129. Suzuki K, Awata S, Matsuoka H. One-year outcome after response to ECT in middle-aged and elderly patients with intractable catatonic schizophrenia. *J ECT* (2004) **20**(2):99–106. doi:10.1097/00124509-200406000-00005
130. Suzuki K, Awata S, Takano T, Ebina Y, Iwasaki H, Matsuoka H. Continuation electroconvulsive therapy for relapse prevention in middle-aged and elderly patients with intractable catatonic schizophrenia. *Psychiatry Clin Neurosci* (2005) **59**(4):481–9. doi:10.1111/j.1440-1819.2005.01402.x
131. Suzuki K, Awata S, Takano T, Ebina Y, Shindo T, Harada N, et al. Adjusting the frequency of continuation and maintenance electroconvulsive therapy to prevent relapse of catatonic schizophrenia in middle-aged and elderly patients who are relapse-prone. *Psychiatry Clin Neurosci* (2006) **60**(4):486–92. doi:10.1111/j.1440-1819.2006.01536.x
132. Hatta K, Miyakawa K, Ota T, Usui C, Nakamura H, Arai H. Maximal response to electroconvulsive therapy for the treatment of catatonic symptoms. *J ECT* (2007) **23**(4):233–5. doi:10.1097/yct.0b013e3181587949
133. Escobar R, Rios A, Montoya ID, Lopera F, Ramos D, Carvajal C, et al. Clinical and cerebral blood flow changes in catatonic patients treated with ECT. *J Psychosom Res* (2000) **49**(6):423–9. doi:10.1016/S0022-3999(00)00190-2
134. Morrison JR. Catatonia: prediction of outcome. *Compr Psychiatry* (1974) **15**(4):317–24. doi:10.1016/0010-440X(74)90053-4
135. McCall WV. The response to an amobarbital interview as a predictor of therapeutic outcome in patients with catatonic mutism. *Convuls Ther* (1992) **8**(3):174–8.
136. Raveendranathan D, Narayanaswamy JC, Reddi SV. Response rate of catatonia to electroconvulsive therapy and its clinical correlates. *Eur Arch Psychiatry Clin Neurosci* (2012) **262**(5):425–30. doi:10.1007/s00406-011-0285-4
137. Malur C, Pasol E, Francis A. ECT for prolonged catatonia. *J ECT* (2001) **17**(1):55–9. doi:10.1097/00124509-200103000-00012
138. Ozgen H, Wijkstra J, Vorstman J. Successful electroconvulsive therapy in a young woman with chronic catatonia. *Primary Care Companion CNS Disord* (2012) **14**(3). doi:10.4088/PCC.11l01328
139. Cupina D, Patil S, Loo C. Chronic catatonic schizophrenia treated successfully with right unilateral ultrabrief pulse electroconvulsive therapy: case report. *J ECT* (2013) **29**(2):134–6. doi:10.1097/YCT.0b013e31827659e4
140. de Silva VA, Lakmini WD, Gunawardena HN, Hanwella R. Chronic catatonia treated with electroconvulsive therapy: a case report. *J Med Case Reports* (2013) **7**:219. doi:10.1186/1752-1947-7-219
141. Gazdag G, Kocsis-Ficzere N, Tolna J. The augmentation of clozapine treatment with electroconvulsive therapy. *Ideggyogy Sz* (2006) **59**(7–8):261–7.
142. DeJong H, Bunton P, Hare DJ. A systematic review of interventions used to treat catatonic symptoms in people with autistic spectrum disorders. *J Autism Dev Disord* (2014) **44**(9):2127–36. doi:10.1007/s10803-014-2085-y
143. Consoli A, Benmiloud M, Wachtel L, Dhossche D, Cohen D, Bonnot O. Electroconvulsive therapy in adolescents with the catatonia syndrome: efficacy and ethics. *J ECT* (2010) **26**(4):259–65. doi:10.1097/YCT.0b013e3181fb3924
144. Cristancho P, Jewkes D, Mon T, Conway C. Successful use of right unilateral ECT for catatonia: a case series. *J ECT* (2014) **30**(1):69–72. doi:10.1097/YCT.0b013e31829a01d3
145. Rhoads JC, Votolato NA, Young JL, Gilchrist RH. The successful use of right unilateral ultra-brief pulse electroconvulsive therapy in an adolescent with catatonia. *Brain Stimul* (2010) **3**(1):51–3. doi:10.1016/j.brs.2009.07.003
146. Kugler JL, Hauptman AJ, Collier SJ, Walton AE, Murthy S, Funderburg LG, et al. Treatment of catatonia with ultrabrief right unilateral electroconvulsive therapy: a case series. *J ECT* (2014). doi:10.1097/YCT.0000000000000185
147. Kellner CH, Popeo DM, Aloysi AS. Electroconvulsive therapy for catatonia. *Am J Psychiatry* (2010) **167**(9):1127–8. doi:10.1176/appi.ajp.2010.10020261
148. Grisaru N, Chudakov B, Yaroslavsky Y, Belmaker RH. Catatonia treated with transcranial magnetic stimulation. *Am J Psychiatry* (1998) **155**(11):1630.
149. Saba G, Rocamora JF, Kalalou K, Benadhira R, Plaze M, Aubriot-Delmas B, et al. Catatonia and transcranial magnetic stimulation. *Am J Psychiatry* (2002) **159**(10):1794. doi:10.1176/appi.ajp.159.10.1794
150. Di Michele V, Bolino F. A novel treatment option of bipolar depression with psychotic and catatonic features. *Gen Hosp Psychiatry* (2006) **28**(4):364–5. doi:10.1016/j.genhosppsych.2006.05.003
151. Kate MP, Raju D, Vishwanathan V, Khan FR, Nair, Thomas SV. Successful treatment of refractory organic catatonic disorder with repetitive transcranial magnetic stimulation (rTMS) therapy. *J Neuropsychiatry Clin Neurosci* (2011) **23**(3):E2–3. doi:10.1176/appi.neuropsych.23.3.E2
152. Trojak B, Meille V, Bonin B, Chauvet-Geliner J-C. Repetitive transcranial magnetic stimulation for the treatment of catatonia: an alternative treatment to electroconvulsive therapy? *J Neuropsychiatry Clin Neurosci* (2014) **26**(2):E42–3. doi:10.1176/appi.neuropsych.13050102

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Received: 30 September 2014; paper pending published: 03 October 2014; accepted: 26 November 2014; published online: 09 December 2014.

*Citation: Sienaert P, Dhossche DM, Vancampfort D, De Hert M and Gazdag G (2014) A clinical review of the treatment of catatonia. Front. Psychiatry **5**:181. doi: 10.3389/fpsyt.2014.00181*

This article was submitted to Schizophrenia, a section of the journal Frontiers in Psychiatry.

frontiers in PSYCHIATRY

ORIGINAL RESEARCH ARTICLE
published: 26 January 2015
doi: 10.3389/fpsyt.2014.00196

Psychomotor retardation in elderly untreated depressed patients

Lieve Lia Beheydt[1]*, Didier Schrijvers[1], Lise Docx[1], Filip Bouckaert[2], Wouter Hulstijn[1] and Bernard Sabbe[1]

[1] *Collaborative Antwerp Psychiatric Research Institute (CAPRI), Antwerp University, Antwerp, Belgium*
[2] *University Psychiatric Center KU Leuven, Kortenberg, Belgium*

Edited by:
Sebastian Walther, University Hospital of Psychiatry, Switzerland

Reviewed by:
Tobias Bracht, Cardiff University, UK
Valentin Johannes Benzing, University Hospital of Psychiatry, Switzerland

***Correspondence:**
Lieve Lia Beheydt, Medical and Health Science Department, Collaborative Antwerp Psychiatric Research Institute (CAPRI), Antwerp University, Campus Drie Eiken – gebouw R D.R.328, Universiteitsplein 1, Antwerp 2610, Belgium
e-mail: lieve.beheydt@uantwerpen.be

Background: Psychomotor retardation (PR) is one of the core features in depression according to DSM V (1), but also aging in itself causes cognitive and psychomotor slowing. This is the first study investigating PR in relation to cognitive functioning and to the concomitant effect of depression and aging in a geriatric population ruling out contending effects of psychotropic medication.

Methods: A group of 28 non-demented depressed elderly is compared to a matched control group of 20 healthy elderly. All participants underwent a test battery containing clinical depression measures, cognitive measures of processing speed, executive function and memory, clinical ratings of PR, and objective computerized fine motor skill-tests. Statistical analysis consisted of a General Linear Method multivariate analysis of variance to compare the clinical, cognitive, and psychomotor outcomes of the two groups.

Results: Patients performed worse on all clinical, cognitive, and PR measures. Both groups showed an effect of cognitive load on fine motor function but the influence was significantly larger for patients than for healthy elderly except for the initiation time.

Limitations: Due to the restrictive inclusion criteria, only a relatively limited sample size could be obtained.

Conclusion: With a medication free sample, an additive effect of depression and aging on cognition and PR in geriatric patients was found. As this effect was independent of demand of effort (by varying the cognitive load), it was apparently not a motivational slowing effect of depression.

Keywords: major depression, elderly, psychomotor retardation, cognition, copying tasks, neuropsychological assessment, medication free

INTRODUCTION

Apart from a depressed mood and lack of interest, psychomotor symptoms are core features of a major depressive episode (2). Recently, a three factor model of depression was found, representing negative effect, anhedonia, and psychomotor change (3). This psychomotor change symptom cluster has an important clinical, diagnostic, pathophysiological, and therapeutic significance in the clinical and scientific approach of Major Depressive Disorder (MDD) (4–8). Psychomotor retardation (PR) has repeatedly been denoted as an important marker of the melancholia subtype of depression (5, 9–11), and as a predictor for treatment response to several types of antidepressant treatment (5). Since psychomotor functioning is the only factor of depression that does not correlate with severity of depression and since it is not predictive for clinical outcome, it is thought to be a dimension defining a separate type (3), though not exclusively the melancholic subtype of depression. PR has been found to be present in other subtypes of depression too (11–19). However, it is not only the presence of PR that is important, the type of slowing and the cognitive share in the PR are thought to be differentiating between subtypes of depression too (20). Hence the importance of investigating psychomotor functioning in depression in relation to cognitive functioning.

Psychomotor retardation appears to be a particularly predominant symptom of late life depression, an organic subtype of geriatric depression with vascular damage of frontal–subcortical circuits and a depressive–executive dysfunction syndrome (21, 22), but also of other atypical depression presentations such as subsyndromal depression (23). As aging itself already causes a substantial psychomotor slowing in healthy elderly (24–26), elderly depressed patients could be expected to show an even more pronounced form of PR. Pier and colleagues (25) hypothesized an additive effect of aging and depression on the psychomotor performance, be it on the basis of a sample of 11 medicated patients. Bonin-Guillaume et al. (27) too found an additive PR effect in 16 patients. The retardation showed to be an addition of two different types of slowing. There was a general slowing in aging, affecting all stages of information processing, and a more specific slowing in depression, affecting the decisional stage and the neuromotor stage, but not the sensory-motor stage. It should be noted, however, that

they did only investigate the reaction time and not the motor time as a measure of psychomotor speed (27). The included patients in both studies were all using psychotropic medication, i.e., antidepressants (selective serotonin re-uptake inhibitors and tricyclic antidepressants) as well as anxiolytics and confounding medication effects were observed (25, 27). Admittedly, polypharmacy is very common in elder age patients, and since these patients are also more sensitive to all kinds of adverse medication induced side-effects, differentiating between the specific effects of depression, age, and medication is particularly difficult, especially as the medication profiles of the subjects in previous studies may have been extremely divergent. Studies on PR in elderly depression are still scarce and show only partial results, because most of these have only measured PR on the basis of cognitive reaction times, without distinguishing and separating out motor slowing (27–30). The two studies that do investigate motor time include only medicated patients (25, 31). All in all, differentiated research of psychomotor symptoms in geriatric depression is still very limited and only exists in medicated clinical cohorts, so that evidence is still missing for the value of these types of symptoms as a diagnostic tool for this subgroup of depressed patients.

Psychomotor retardation not only involves motor processes, but also cognitive processes. Indeed, the term PR "not only encompasses the output of muscle contractions, but also the wider involvement of perceptual processes and cognitive-control mechanisms" (5) (p. 14). Indeed, several cognitive sub-processes contribute to the psychomotor processing. Studies on neuropsychological functioning in late life depression generally mention processing speed and executive function as the main cognitive impairments in MDD in the elderly (32, 33). Yet, PR and executive functioning are not correlated, indicating that cognitive retardation is not the sole explanation of PR (34). It has been suggested that retardation in executive function is merely the consequence of reduced processing speed (35–37). However, Sexton et al. (38) found that executive deficits could not be fully explained by general impairments in processing speed. Controlling for processing speed, Dybedal et al. (32) still found impaired executive function in elderly depressed compared to healthy controls. Considering that both processing speed and executive functioning are the cognitive hallmarks of depression, they will be treated separately here in relation to psychomotor measures. Since executive function and PR are not correlated, it would be interesting to figure out whether depression severity without interfering medication effects, has a specific impact on cognitive and psychomotor functioning, respectively.

The current study aims to measure cognitive and psychomotor functioning in a sample of unmedicated depressed elderly, applying objective psychomotor, and cognitive assessment methods. In accordance with previous studies (25, 28), it is hypothesized that unmedicated elderly depressed patients will perform worse both on the cognitive and psychomotor tasks. Different cognitive and psychomotor measures will be applied to shed a light on different cognitive factors that may influence PR, most importantly processing speed, but also inhibition and interference resistance, cognitive flexibility, and memory. With the objective measures of PR, the cognitive reaction time, i.e., the initiation time of a movement and the reinspection time, the time needed to verify the stimuli, will be separated from the motor time, i.e., the real movement time. Finally, the effect of cognitive load in PR will be tested by experimentally varying the complexity of the stimuli of the copying task to investigate the interaction of cognition and motor functioning in PR.

MATERIALS AND METHODS

STUDY POPULATION

Twenty-eight non-demented (Mini Mental State Examination Score > 24) elderly (age >60) in- and out-patients with unipolar single episode or recurrent MDD, meeting DSM-IVTR criteria (2), were compared to 20 healthy controls, matched for age, gender, education, and vascular risks (diabetes, hypertension, smoking, obesity, and hyperlipidemia). Patients with a MMSE score under 24, the consensus cut-off score for probable dementia (39–41), were excluded. Depression was identified using the DSM-IVTR criteria and the severity of depression was assessed by means of the Geriatric Depression Scale (GDS). A minimum score of 11 on the GDS was required for inclusion of patients. Patients taking medication with important psychotropic impact such as psychopharmacological treatments, but also antihistaminics and anticholinergics for instance, were excluded. For every type of disallowed or concomitant medication, the drug free period before testing was specified. For most antidepressants, a wash-out period of 1 week prior to baseline was applied, with the exception of fluoxetine (5 weeks), fluvoxamine (2 weeks), and monoamine oxidase inhibitors (2 weeks). Any anxiolytics (including benzodiazepines) and hypnotics (except Zolpidem, Zopiclone, or Zaleplon) were disallowed within the last week prior to testing. Patients and controls suffering from any medical condition [e.g., Parkinson's disease, dementia, psychotic disorders, mental retardation, substance- or alcohol abuse, organic mental disorders due to a general medical condition as defined in the DSM-IV-TR (2)] that might affect fine motor or cognitive processes were excluded, as were patients with personality disorders that might compromise the study. All participants were native Dutch speakers and had given their informed consent after the study was fully explained to them. The study was carried out consistent with the latest version of the Helsinki Declaration (42) and was approved by the medical ethics committee of the participating hospitals.

ASSESSMENTS AND TASKS

All participants performed an extensive cognitive and psychomotor test battery (see below). All testing, for patients and for healthy controls, took place in the afternoon.

Clinical assessment

Clinical depression severity was assessed using the GDS (30 items) (43) whereas the State and Trait Anxiety Inventory (STAI 1 and STAI2) (44) informed about the degree of subjective anxiety symptoms. Both tests were also applied to the controls. The 15-item Salpêtrière Retardation Rating Scale (SRRS) (45) was administered to assess the subjective, rated level of PR.

Psychomotor tasks

For the objective psychomotor assessment (46, 47), participants carried out drawing tasks. Subjects were asked to copy figures from

a computer screen with the use of a special pressure-sensitive pen and a digitizer (48). A full description of the set up as shown in **Figures 1A,B** can be found in Pier et al. (25).

Line and figure copying task. In the Line Copying Task (LCT; **Figure 1A**), patients had to draw a line in one of four directions (horizontal, vertical, or one of the two diagonals) as quickly as possible. In the Figure Copying Task (FCT; **Figure 1B**), they had to copy figures consisting of four line segments with varying complexity, some were well-known letters, other were familiar figures and the third kind were less familiar patterns. The stimulus (line or figure) appeared on the screen when the participant placed the pen tip in the start circle at the bottom left of the box in which the stimulus had to be copied. As soon as participants started drawing, the figure disappeared from the screen. However, there was the possibility (which was not encouraged) to reinspect the figure by retouching the start circle. To end a trial, participants had to place the pen in the stop circle at the upper right corner of the box. Initiation time, the time between the presentation of the stimulus and the start of the first drawing movement, was measured. Also the motor time, the time from the start of the first drawing movement to the end of the last drawing movement, was calculated. In the second task, the reinspection time, the time from retouching the spot to resuming starting the drawing was also determined. Time to reinspect was not included in the motor time.

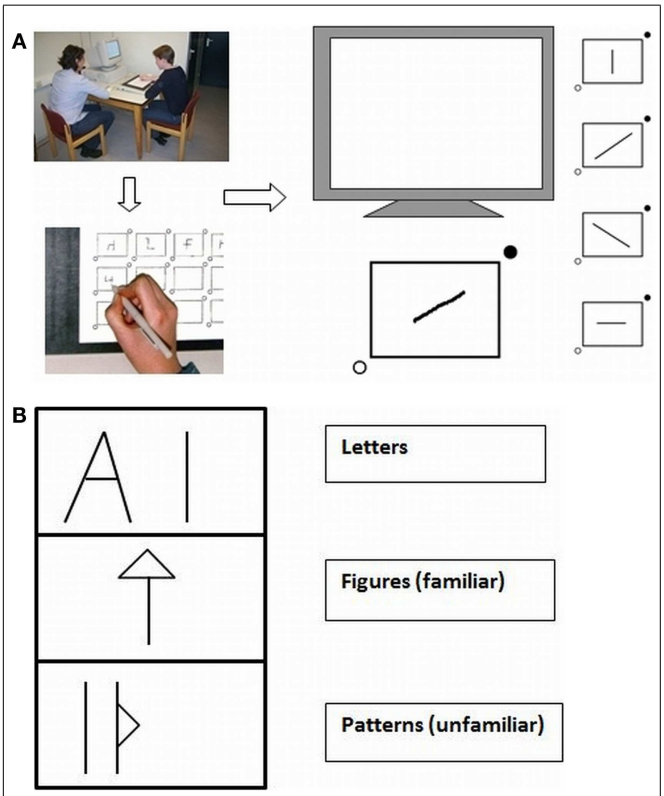


FIGURE 1 | (A,B) Set up **(A)** of the line and complex figure copying task **(B)** with pressure-sensitive digitizer.

Symbol-digit substitution test. The same recording techniques were used as with the copying tasks (49–51). This made it possible to differentiate between a cognitive and a psychomotor component apart from the general measure of information processing speed. The subjects had to substitute symbols by digits during a period of 90 s, using a key consisting of nine symbol–digit pairs. The following variables were analyzed: raw scores, i.e., the number of correct answers, matching time, representing mean pen-up time, and pause time between two successive digits (comparable to the initiation time in the copying tasks), and writing time, representing the time needed to write a digit (comparable to motor time).

Cognitive tasks

Wisconsin card sorting task. In the Wisconsin card sorting task (WCST) (52), which is primarily intended to measure cognitive flexibility, an executive function, four key cards were presented with geometric figures that vary according to three perceptual dimensions (color, form, and number). The subjects had to discover the correct sorting principle by trial and error. After each choice they got a feedback (right or wrong). Once the participant made a correct choice, this sorting principle had to be maintained across changing stimulus conditions while ignoring the other – now irrelevant – stimulus dimensions. After 10 consecutive correct matches, the classification principle changed without warning. As the WCST is not timed, sorting continued until all cards were sorted or a maximum of six correct sorting criteria had been reached. Index of the participant's performance was the number of categories completed (53–56). However, since some patients did not even complete one category, executive functions such as switching could not be measured.

Stroop color-word test. The Stroop color-word test (57, 58) is a cognitive test that requires participants to firstly read the names of colors printed in black ink (trial 1), then name printed colors (trial 2) as quickly as possible without making errors and then naming the color of a word in which it is printed (trial 3). The test measures the individual's ability to suppress task-irrelevant responses (i.e., the tendency to read the color name rather than name the color) and ability to maintain attention and concentration (59). The Stroop interference score was calculated as the time taken to name colors in trial 3 minus the time taken to name color names in trial 2. A higher Stroop interference score thus refers to the degree of interference caused by suppressing the habit of reading words in order to name colors; a higher score reflects poorer performance (59).

15-Words tests. In the 15-words task, a verbal memory task (60), subjects were presented 5 times a list of 15 words, which they had to reproduce. After an interval of 20 min, the experimenter asked to reproduce the memorized words once more. Afterward they had to recognize in a list of 30 words, which were the words they had studied. Only the sum of correct recalls has been recorded (Verbal Memory Total). The delayed recall was scored as Verbal Memory Recall. For the Verbal Memory Recognition too, only correct recognitions were scored.

STATISTICAL ANALYSIS

Statistical analysis of the data was performed using SPSS 17.00 and consisted of a General Linear Method (GLM) multivariate analysis

of variance to compare the psychomotor and cognitive outcomes of the two groups. To measure the effect of cognitive load in the figure copying tasks, a GLM Repeated Measures Analysis of Variance with Group (MDD, Controls) as between-subjects factor and Complexity (letters, figures, and patterns) as within-subjects factor was performed. In addition, bivariate Pearson correlations were computed between severity of depression and the other clinical, cognitive, and psychomotor measures. Significance level was set at $p < 0.05$.

RESULTS

DEMOGRAPHIC AND CLINICAL VARIABLES

As can be seen in **Table 1**, there were no significant differences between groups on demographical variables. Patients were significantly more depressed, more anxious (as well state as trait anxiety), and showed more psychomotor retardation (SSRS) and cognitive impairment (MMSE). Severity of depression correlated with none of the cognitive and psychomotor measures, only with clinical measures of state anxiety (r GDS-STAI I = 0.524, $p = 0.006$) and slightly with the clinical rating of retardation (r GDS-SRRS = 0.418, $p = 0.047$).

COGNITIVE AND PSYCHOMOTOR PERFORMANCE

Patients performed significantly worse than controls on all cognitive measures. For an overview, see **Table 2**. The largest effects are found for the number of correct filled in items on the symbol-digit substitution test (SDST) (Cohen's $d = 1.37$) (61), the matching time of SDST (Cohen's $d = 0.94$), the Wisconsin number of categories completed (Cohen's $d = 1.40$), and the total recall of the verbal memory test (Cohen's $d = 0.96$). The measures of the perseverative errors and non-perseverative errors in the Wisconsin task had to be left out because they proved meaningless, as patients could not even complete one category. The impaired learning capacity is confirmed by the verbal memory scores. As can be seen in the table, the Stroop tasks too almost reached significance on the 0.01 level. In general, however, the significance was lowered by the difference in variance between patients and healthy controls, with a larger variance in the patient scores, except for the WCST. The latter exception can presumably be explained by a floor effect, as patients did not even manage to learn one category. The difference in SDST total correct, the measure of processing speed, reveals that a general retardation of processing speed is a central feature of elderly depression. Still on the SDST, both the matching and

Table 1 | Demographic and clinical variables of patients and controls.

	Patients ($N = 28$)	Controls ($N = 20$)	F	p	Cohen's d
Age	74.71 (7.56)	71.95 (5.14)	2.01	0.163	
Male/female	4/24	5/15	$X^2 = 0.879$	0.348	
MMSE	25.52 (3.80)	28.30 (1.38)	9.73	0.003	0.97
GDS	17.58 (4.46)	4.15 (2.50)	145.83	<0.001	3.71
STAI 1	51.93 (11.38)	34.50 (7.83)	34.98	<0.001	1.82
STAI 2	51.00 (10.25)	34.45 (7.65)	36.81	<0.001	1.83
SRRS	16.44 (8.74)	2.30 (1.92)	50.16	<0.001	2.23

Standard deviations are shown in parentheses.

Table 2 | Mean performance levels of patients and controls on cognitive and psychomotor measures.

	Patient	Control	F	P	Cohen's d
Neuropsychological tests					
SDST number correct	43.63 (9.38)	27.52 (13.46)	19.41	<0.001	1.37
SDST_matching time	3.42 (2.90)	1.47 (0.45)	8.44	0.006	0.94
SDST_writing time	1.17 (1.08)	0.66 (0.13)	4.23	0.047	0.67
Stroop card 1	63.43 (24.10)	47.32 (11.21)	7.19	0.011	0.83
Stroop interference	111.43 (110.54)	46.11 (21.42)	37.23	0.016	0.80
WCST *N* categories completed	0.65 (0.83)	2.00 (1.12)	19.16	<0.001	1.40
Verbal memory total	26.71 (11.91)	36.32 (7.77)	9.55	0.003	0.96
Verbal memory recall	4.59 (3.24)	6.63 (3.06)	4.63	0.037	0.53
Verbal memory recognition	22.72 (4.21)	25.72 (2.61)	7.15	0.011	0.86
Psychomotor tasks					
LCT_initiation time (s)	1.46 (1.00)	0.97 (0.17)	4.49	0.040	0.65
LCT_movement time (s)	0.73 (0.38)	0.47 (0.17)	7.78	0.008	0.86
FCT_initiation time (s)	2.98 (1.03)	2.60 (0.85)	1.67	0.203	0.39
FCT_reinspection time (s)	0.41 (0.66)	0.10 (0.19)	3.99	0.053	0.60
FCT_movement time (s)	3.94 (2.36)	2.38 (1.15)	7.03	0.011	0.79

Standard deviations are shown in parentheses.

the writing time were significantly higher in patients, indicating cognitive as well as psychomotor slowing on this task.

As for performance on the copying tasks, patients' initiation time was found to be impaired on the LCT, but not on the FCT, whereas movement time was significantly higher in patients than in controls on both the LCT and the FCT. Analysis reveals a more significant difference between the healthy and the depressive elderly on the movement time compared to the initiation time. Finally, patients reinspected significantly longer than controls on the FCT.

As shown in **Figure 2**, increasing figure complexity in the FCT for increased cognitive load, resulted in a significantly increased initiation time ($F = 10.38$, $p = 0.0002$) and execution time ($F = 10.721$, $p = 0.0002$) for both patients and controls and in a significantly longer reinspection time ($F = 3.89$, $p = 0.029$) in the patient group. However, the increased cognitive load affected patients' psychomotor performance more than that of controls, except for the initiation time (IT, **Figure 2A**: $F = 1.27$, $p = 0.267$, ns; MT, **Figure 2B**: $F = 10.721$, $p = 0.002$; and Reinspection, **Figure 2C**: $F = 4.98$, $p = 0.031$). Both patients and healthy controls initiated the drawing movements immediately, but the patients faltered while drawing and recurred more often to the stimuli.

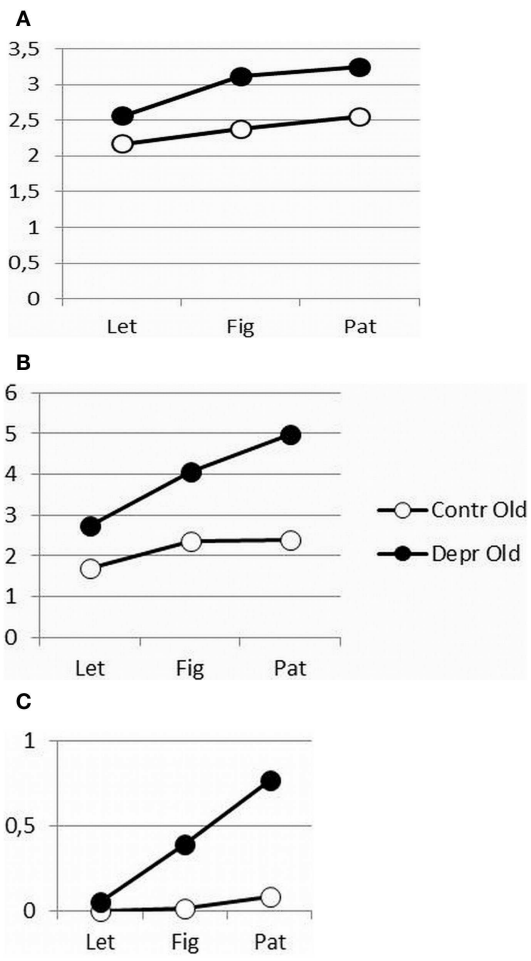


FIGURE 2 | (A–C) Differences in initiation time **(A)**, movement time **(B)**, and reinspection time **(C)** as a function of complexity between depressive patients and healthy controls.

DISCUSSION

In this study, we investigated psychomotor and cognitive performance as an effect of depression in an elderly medication free depressed sample, with both objective motor and cognitive measures. To find out the impact of a cognitive factor in PR, we experimentally varied the amount of cognitive load in psychomotor functioning. Because Tarbuck and Paykel (28), on the basis of an unmedicated sample, assumed that retardation due to age is associated with timed tasks only and that PR due to depression is associated with the complexity of the task, we chose to use a non-timed psychomotor task to see whether the difference still showed. The geriatric depressed patients (as a group) were found to be significantly slower on almost all psychomotor measures, as reflected in high SRRS scores as well as in inferior outcomes on most of the copying tasks, compared to the outcomes recorded for the matched healthy controls. In general, this is in line with previous studies in depressed samples that applied the same assessment methods, in elderly (25) and in younger patients (14, 62–64). However, the sample in this medication free population shows peculiarities of slowing that, moreover, provide valuable insights into the very specific interaction of cognitive and psychomotor slowing in the convergence of depression and aging.

When varying the complexity of figures to copy and thus varying the cognitive load, it is strikingly the motor time that shows the most significant interaction effects of group (depressive elderly versus healthy elderly) and complexity; the reinspection time is less significant, the initiation time not at all. Patients start copying immediately, irrespective of the complexity of the task. Nevertheless, in cognitive more difficult motor tasks, the movements of the depressed elderly become slower or more hesitating, with some more reinspection. Apparently, various cognitive and motor processes are involved in figure copying. Initiation times are assumed to mainly reflect the cognitive processes and encompass the attention for and the perception of the stimulus figure, as well as the storage of the representation in working memory, but also the programing and planning of the first drawing movement and the activation of motor programs that initiate the muscle to start drawing (14).

Scrutinizing the differential effect of increased task difficulty on movement time and initiation time leads to an adaptation of the notion of initiation time. Traditionally, "initiation time" has been defined as a "cognitive" time, different from "motor" time, the time of execution of the movement (14, 25, 64). The fact that more complex tasks lead to longer motor times but not to longer initiation times reveals a cognitive aspect in the motor time. The initiation time, in turn, should be perceived as a simple reaction time, a measure of general processing speed and cognitive reserve. This measure of processing speed in the performed tasks was merely measuring the time of "decision to start," which is not different for simple and complex tasks. "Decisions are made by accumulating noisy stimulus information until sufficient information for a response [for a response criterion] is obtained" (65). Admittedly, the initiation time of patients was longer compared

to controls in copying simple lines. This could, however, be linked to changes in white matter integrity of the motor system (66). In a study of Walther et al. (66), patients with MDD differed from healthy controls in a loss of frontal integrity, which was linearly related to a lower activity level. An alternative explanation could be that there was already a ceiling effect of slowing of initiation time in simple tasks in patients. Slower subjects have already more influence of prefrontal executive control in simple tasks for successful performance (67). Evidence has been found indeed for different associations between structures and behavior in depressive patients and healthy controls (66). Bracht et al. found altered cortico-cortical white matter motor pathways, and concluded that these may contribute to movement initiation in MDD (68). A more refined gradation of cognitive reserve impairment can still be made by involving the motor time assessed in the copying task. The execution of a movement while planning and preparing the next is a dual task recruiting more brain regions in parallel (69). The impaired efficiency of interaction between the dorsolateral prefrontal cortex and the pre-supplementary motor area by altered white matter organization of the pathway (68) needs more prefrontal executive higher order compensation (69). We presume that this hierarchical plasticity of the brain principle with higher order integration for output with lower order deficits is also responsible for disbalanced motor control with more activation of (higher order) right orbitofrontal cortex and less activation of the (lower order) left supplemental motor area in higher activity level (70).

The predominantly dopaminergic dysregulation of cognition and motor functioning by striatal dopamine transporters (71, 72) has motivational correlates too (73), manifested in decisional anhedonia (74). Lowered mesolimbic dopamine projections in the nucleus accumbens (74) and overstimulation of nucleus accumbens adenosine receptors (75) change the GABAergic signals that relay through the ventral tegmentum, associated with motor control, and the substantia nigra, associated with reward cognition, resulting in changed effort-based decision making with decreased perceived net-value under increasing response costs (74). These response costs can be increased by task complexity or higher activity level. Limitations of these findings are the important age and sex influences in dopaminergic neuromodulating influences (72), which urge for further investigation.

Clearly, figure copying is different from the separate cognitive measures in standard cognitive testing. Even the SDST tends to reflect higher order cognitive, memory related functions more than it does psychomotor speed (14, 76). The bigger higher order executive cognitive load of searching for a number in the legend code, memorizing the found digit and subsequently performing the initiation and planning of writing the digit in the SDST and the relative easiness of writing a well-known automatized digit compared to an unknown pattern, may also explain the difference in effect size of the matching time of SDST (Cohen's $d = 0.94$) and the initiation time of the figure copying (Cohen's d LCT initiation $= 0.65$; Cohen's d FCT initiation $= 0.39$). Furthermore, patients performed worse than controls on all cognitive measures in the standard cognitive tasks. It must be remembered, however, that above all, the more cognitive executive aspects show cumulative effects of aging and depression, except in the WCST. The lack of interaction effect in the WCST is clearly a result of the missing measure of executive function due to the patients' inability to learn even one category. Measuring adaptation and perseveration thus became impossible.

All in all, the difference in slowing as a result of increasing cognitive load may be explained as an effect of cognitive aspects in psychomotor functioning. Presumably, the cognitive component of PR is different in nature and involves more motor circuitry involvement than that measured by the standard cognitive tasks.

The present results suggest that PR observed in the patient group was caused by both a cognitive and a motor factor, as, respectively, most matching times and writing times were higher in patients. In order to further scrutinize the possible cognitive effect, we compared the current results *post hoc* to the ones obtained in a similar study in an adult population of depressed medicated patients and in healthy controls (18–60 years). This way, we could also gain some insight into possible interaction effects of age and depression and we could determine whether there was a link with cognitive functioning. In **Figure 3**, we have presented the results of this *post hoc* comparison. Since adult medicated patients appear to be even less retarded than elderly depressive unmedicated patients, these results only corroborate the hypothesis of an aging effect in depression. The overall comparison in **Figure 3** reveals a clear effect of depression in all ages, both, for the cognitive measures (**Figure 3A**: F SDST matching time $= 36.40$, $p < 0.001$; F SDST writing time $= 22.36$, $p < 0.001$; F Stroop card $1 = 25.58$, $p < 0.001$; F Stroop interference $= 31.24$, $p < 0.001$; and F WCST N categories completed $= 10.54$, $p = 0.001$) and for the psychomotor measures (**Figure 3A**: F LCT initiation time $= 24.29$, $p < 0.001$; F LCT movement time $= 13.83$, $p < 0.001$; F FCT initiation time $= 8.54$, $p = 0.004$; F FCT reinspection time $= 14.71$, $p < 0.001$; and F FCT movement time $= 25.35$, $p < 0.001$). An aging effect is equally obvious, also in both, in cognitive measures (**Figure 3A**: F SDST matching time $= 29.96$, $p < 0.001$; F writing time $= 45.32$ $p < 0.001$; F Stroop card $1 = 16.21$, $p < 0.001$; F Stroop interference $= 39.19$, $p < 0.001$; and F WCST N categories completed $= 31.21$, $p < 0.001$) and in psychomotor measures (**Figure 3B**: F LCT initiation time $= 8.55$, $p = 0.004$; F LCT movement time $= 3.22$, $p = 0.074$; F FCT initiation time $= 144.70$, $p < 0.001$; FCT reinspection time $= 19.37$, $p < 0.001$; and FCT movement time $= 22.02$, $p < 0.001$). A calculation of possible interaction effects of aging and depression in the GLM test indicates that only the matching time and the writing time of the SDST and the Stroop interference show interaction effects (F SDST matching time $= 11.80$ $p = 0.001$; F SDST writing time $= 9.50$, $p = 0.002$; F Stroop card $1 = 1.57$, $p = 0.211$; F Stroop interference $= 12.65$, $p < 0{,}001$; F WCST $= 0.63$, $p = 0.429$). In the psychomotor measures, only the reinspection time shows a slightly significant interaction effect (F LCT initiation time $= 2.10$, $p = 0.149$; F LCT movement time $= 0.001$, $p = 0.979$; F FCT initiation time $= 0.04$, $p = 0.837$; F FCT reinspection time $= 6.35$, $p = 0.12$; and F FCT movement time $= 3.09$, $p = 0.80$). However, this effect was not reflected in the results. The significance was diminished by the much larger variance on the reinspection times of the complex figure copying task in the elder population. Indeed, there is an overall increase of variance in the elderly, especially in psychomotor tasks where motor and cognitive aspects coincide

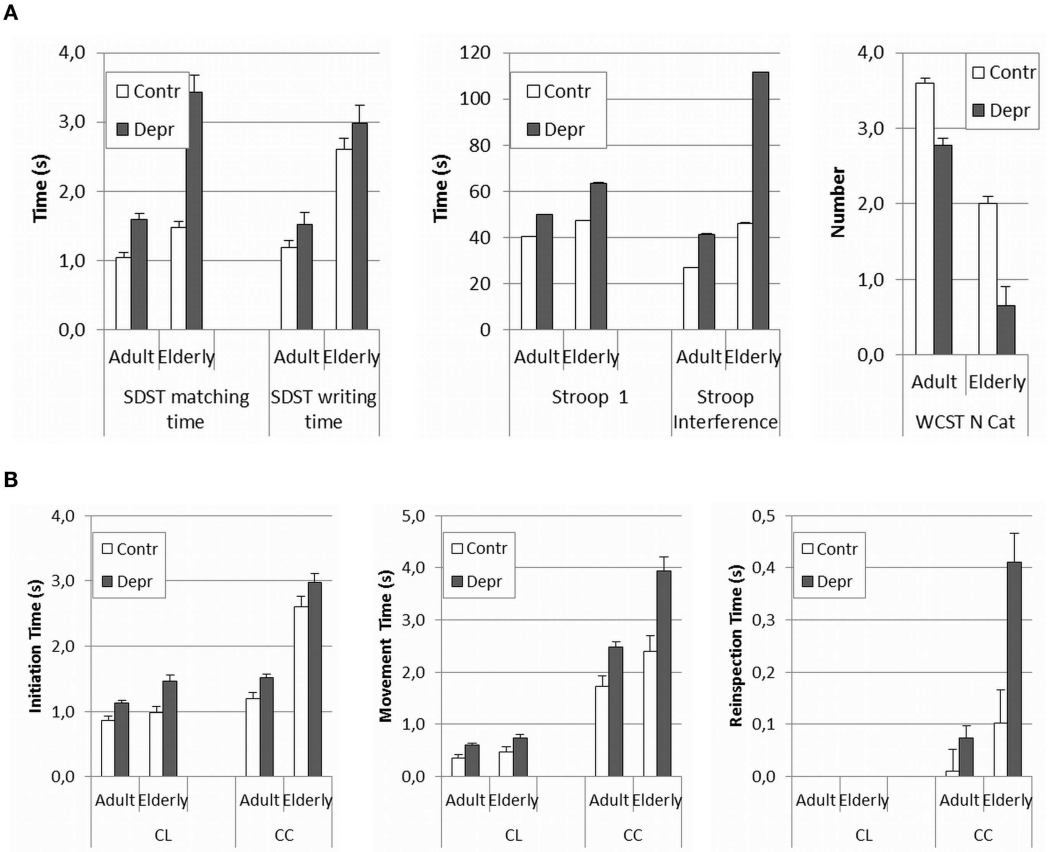


FIGURE 3 | (A,B) Comparison of psychomotor and cognitive measures between healthy and depressed elderly against the background of previous research with the same tasks in adults. Because of limited competence of the population, with the elderly the copying task consisted of just four lines, whereas with the adults a task with eight lines was used. To make the results comparable, recalculations were made for the adult scores based on the mean time for four lines. Separate times for each line were available.

(SDST matching, writing time, and complex figure reinspection). Overlooking the overall results leads to the assumption that the interaction of depression and aging reveals itself in executive functioning and in the interaction of cognitive and psychomotor functioning. The main comparison of the Cohen's *d* effect sizes in the elderly and adult group shows that the effect of depression is always bigger in elderly. The relatively small difference between the effect sizes of the adults and the elderly however, is explained by the large variance in older groups, which limits the found intergroup effects. Surprisingly, the effect sizes of initiation time of the copying tasks show the reverse direction; it is bigger in adults. Evidently, these results need to be confirmed by direct comparative research.

The present study not only confirms the results of a similar study by Pier et al. (25), it also provides a valuable contribution in its own right, as it overcomes some of the restrictions of the earlier study. Whereas, the study by Pier et al. (25) was a small sample study ($n = 11$) in which patients were taking medication that could have impacted the results, the present study is unique in that it involves only patients that are free of psychotropics. The importance of the latter condition is apparent from the fact that in the Pier et al. study (25) correlations were found between the use of antidepressants and anxiolytics on the one hand, and several psychomotor outcomes on the other. With our larger medication free sample, we succeeded in replicating the results of Pier et al. (25), corroborating their preliminary results concerning the presence of PR in elderly depressed patients, independent of medication status. Apart from that, the present study revealed an interesting difference between medicated and unmedicated patients. In comparison to the control groups (healthy aged, younger depressed), the pattern of interaction between the degree of slowing and the cognitive complexity of the task in the unmedicated elderly sample seemed to be the reverse. In the unmedicated elderly sample, PR was proportionately more visible in more complex tasks (copying more complex figures, less familiar figures) than in copying simple lines. In the medicated sample, on the contrary, the PR was more obvious in comparison with the other groups in the simple copying task than in the more complex tasks (63) (p. 24). This result is in line with the suggestion by Caligiuri et al. (20) that retardation caused by medication is predominantly neuromotor retardation, i.c. abnormal velocity, as opposed to the psychomotor slowing in depression, in which the cognitive factor is more important. Benzodiazepines, opioids, anticholinergics, but also tricyclic antidepressants (77) often elicit modest or

more pronounced psychomotor or cognitive impairments (78). These findings support the diagnostic relevance of the quality of slowing in major depression, in aging and in a broad range of psychopathological disorders.

Notwithstanding the relatively small sample size, the reported effects were robust. The very restrictive inclusion criteria determining the sample size were introduced because of the high comorbidity of depression and the considerable use of medication in the elderly and because of the numerous possible cognitive – and psychomotor – side-effects of somatic and degenerative diseases. To avoid such confounding cognitive effects a selection of elderly depressive patients imposed itself. Despite the fact that such a strict selection can hardly be seen as representative for the "natural" population, it afforded a unique opportunity to rule out possible medication and comorbidity effects and to obtain an unbiased view on the differential PR effects of depression in the elderly. A limitation of this study could be that cardiovascular disease, a recognized cause of psychomotor slowing in elderly due to white matter lesions (WML) (79), was only excluded after introducing a questionnaire for the patient and the treating physician. The sample of patients was, however, too small to introduce cardiovascular disease as a covariate. MRI volume measures of WML could have provided a more objective measure of vascular risks causing neuromotor slowing (80), but the primary focus of the present investigation was to reveal the different types of slowing factors. Admittedly, Hickie et al. (79), who combined clinical, neuropsychological, magnetic resonance imaging, and single photon emission computerized tomography, found that the percentage caudate nucleus regional cerebral blood flow was associated with psychomotor slowing and presence of WML. Even if their neuropsychological measures included only reaction times and did not offer an integrated view of cognitive and motor psychomotor slowing (cf. the movement time of complex figures in the present study), they still found 25% of the variance explained by "depression." Consequently, they concluded that "while psychomotor slowing is determined in part by subcortical changes, other cortical and illness-dependent factors are likely to be relevant" (79). This result confirms the necessity of a detailed neuropsychological analysis of psychomotor functioning in the explorative stage. Such analysis is essential to unravel the complexity of the symptom of slowing and to better understand its physiopathology. Further research with more direct neurobiological measures will have to objectify relative shares of biological and functional aspects in different types of slowing. Since it has become clear that biological aspects like WML account for age-related declines, irrespective of depression (81), an interdisciplinary approach of PR in elderly depressed seems to be in order.

REFERENCES

1. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders 5th ed.* Washington, DC: American Psychiatric Association (2013).
2. American Psychiatric Association. *APA Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV).* Washington, DC: American Psychiatric Association (1994).
3. Vrieze E, Demyttenaere K, Bruffaerts R, Hermans D, Pizzagalli D, Sienaert P, et al. Dimensions in major depressive disorder and their relevance for treatment outcome. *J Affect Disord* (2014) **155**:35–41. doi:10.1016/j.jad.2013.10.020
4. Sobin C, Sackeim HA. Psychomotor symptoms of depression. *Am J Psychiatry* (1997) **154**:4–17. doi:10.1176/ajp.154.1.4
5. Schrijvers D, Hulstijn W, Sabbe BCG. Psychomotor symptoms in depression: a diagnostic, pathophysiological and therapeutic tool. *J Affect Disord* (2008) **109**:1–20. doi:10.1016/j.jad.2007.10.019
6. Bennabi D, Vandel P, Papaxanthis C, Pozzo T, Haffen E. Psychomotor retardation in depression: a systematic review of diagnostic, pathophysiologic, and therapeutic implications. *Biomed Res Int* (2013) **2013**:158746. doi:10.1155/2013/158746
7. Widlöcher D, Ghozlan A. The measurement of retardation in depression. In: Hindmarch I, Stonier PD, editors. *Human Psychopharmacology: Measures and Methods.* New York: Wiley (1989). 2 p.
8. Widlöcher DJ. Psychomotor retardation: clinical, theoretical, and psychometric aspects. *Psychiatr Clin North Am* (1983) **6**(1):27–40.
9. Parker G. Classifying depression: should paradigms lost be regained? *Am J Psychiatry* (2000) **157**:1195–203. doi:10.1176/appi.ajp.157.8.1195
10. Pier MPBI, Hulstijn W, Sabbe BGC. Differential patterns of psychomotor functioning in unmedicated melancholic and nonmelancholic depressed patients. *J Psychiatric Res* (2004) **38**:425–35. doi:10.1016/j.jpsychires.2003.11.008
11. Benazzi F. Psychomotor changes in melancholic and atypical depression: unipolar and bipolar-II subtypes. *Psychiatry Res* (2002) **112**(3):211–20. doi:10.1016/S0165-1781(02)00241-X
12. Gupta RK. Major depression: an illness with objective physical signs. *World J Biol Psychiatry* (2009):196–201. doi:10.1080/15622970902812072
13. Niculescu IIIAB, Akiskal HS. Proposed endophenotypes of dysthymia: evolutionary, clinical and pharmacogenomics considerations. *Mol Psychiatry* (2001) **6**(4):363–6. doi:10.1038/sj.mp.4000906
14. Schrijvers D. *Monitoring Slow Motion: Action Disturbances in Major Depressive Disorder.* Antwerpen: University of Antwerp UA Faculteit Geneeskunde (2009).
15. Smith MJ, Brebion G, Banquet JP, Cohen L. Retardation of mentation in depressives: Posner covert orientation of visual attention test. *J Affect Disord* (1995) **35**(3):107–15. doi:10.1016/0165-0327(95)00044-5
16. Widlöcher D. Retardation: a basic emotional response? In: Davis JH, Maas JW, editors. *The Affective Disorders.* Washington, DC: American Psychiatric Press (1983). p. 165–81.
17. Buyukdura J, McClintock S, Croarkin P. Psychomotor retardation in depression: biological underpinnings, measurement, and treatment. *Prog Neuropsychopharmacol Biol Psychiatry* (2011) **35**:395–409. doi:10.1016/j.pnpbp.2010.10.019
18. Akiskal HS. Dysthymia and cyclothymia a century after Kraepelin. *J Affect Disord* (2001) **62**(1–2):17–31. doi:10.1016/S0165-0327(00)00347-5
19. Blackburn IM. Mental and psychomotor speed in depression and mania. *Br J Psychiatry* (1975) **126**:329–35. doi:10.1192/bjp.126.4.329
20. Caligiuri M, Elswanger J. Motor and cognitive aspects of motor retardation in depression. *J Affect Disord* (2000) **57**:83–93. doi:10.1016/S0165-0327(99)00068-3
21. Bella R, Pennisi G, Cantone M, Palermo F, Pennisi M, Lanza G, et al. Clinical presentation and outcome of geriatric depression in subcortical ischemic vascular disease. *Gerontology* (2010) **56**(3):298–302. doi:10.1159/000272003
22. Alexopoulos GS, Meyers BS, Young RC, Kakuma T, Feder M, Einhorn A, et al. Recovery in geriatric depression. *Arch Gen Psychiatry* (1996) **53**(4):305–12. doi:10.1001/archpsyc.1996.01830040039008
23. Judd LL, Rapaport MH, Paulus MP, Brown JL. Subsyndromal symptomatic depression: a new mood disorder? *J Clin Psychiatry* (1994) **55**(4):18–28.
24. Cerella J, Rybash J, Hoyer W, Commons ML. *Adult Information Processing: Limits on Loss.* California: Academic Press (1993).
25. Pier MPBI, Hulstijn W, Sabbe BGC. Psychomotor retardation in elderly depressed patients. *J Affect Disord* (2004) **81**:73–7. doi:10.1016/j.jad.2003.08.002
26. Seidler RD, Bernard JA, Burutolu TB, Fling BW, Gordon MT, Gwin JT, et al. Motor Control and Aging: links to age-related brain structural, functional and biochemical effects. *Neurosci Biobehav Rev* (2010) **34**(5):721–33. doi:10.1016/j.neubiorev.2009.10.005
27. Bonin-Guillaume S, Hasbroucq T, Blin O. Mise en evidence d'un ralentissement psychomoteur spécifique à la depression chez le sujet agé. *Psychol Neuropsychiatr Vieil* (2008) **6**(2):137–44. doi:10.1684/pnv.2008.0121
28. Tarbuck AF, Paykel ES. Effects of major depression on the cognitive function of younger and older subjects. *Psychol Med* (1995) **25**:285–95. doi:10.1017/S0033291700036187
29. Hart RP, Kwentus JA. Psychomotor slowing and subcortical-type dysfunction in depression. *J Neurol Neurosurg Psychiatry* (1987) **50**(10):1263–6. doi:10.1136/jnnp.50.10.1263

30. Nebes RD, Halligan EM, Rosen J. Reynolds, CF3rd. Cognitive and motor slowing in Alzheimer's disease and geriatric depression. *J Int Neuropsychol Soc* (1987) **4**(5):426–34.
31. Beats BC, Sahakian BJ, Levy R. Cognitive performance in tests sensitive to frontal lobe dysfunction in the elderly depressed. *Psychol Med* (1996) **26**:591–603. doi:10.1017/S0033291700035662
32. Dybedal GS, Tanum L, Sundet K, Gaarden TL, Bjølseth TM. Neuropsychological functioning in late-life depression. *Front Psychol* (2013) **4**:381. doi:10.3389/fpsyg.2013.00381
33. Naismith SL, Norrie LM, Mowszowski L, Hickie IB. The neurobiology of depression in later-life: clinical, neuropsychological, neuroimaging and pathophysiological features. *Prog Neurobiol* (2012) **98**(1):99–143. doi:10.1016/j.pneurobio.2012.05.009
34. Baudic S, Benisty S, Dalla Barba G, Traykov L. L'atteinte des fonctions exécutives chez la personne âgée présentant un épisode dépressif majeur unipolaire sévère: influence du ralentissement dépressif [Impairment of executive function in elderly patients with major unipolar depression: influence of psychomotor retardation]. *Psychol Neuropsychiatr Vieil* (2007) **5**(1):65–71 [Original article in French]. doi:10.1684/pnv.2007.0036
35. Butters M, Whyte E, Nebes R, Begley A, Dew M, Mulsant B, et al. The nature and determinants of neuropsychological functioning in late-life depression. *Arch Gen Psychiatry* (2004) **61**:587–95. doi:10.1001/archpsyc.61.6.587
36. Sheline YI, Barch DM, Garcia K, Gersing K, Pieper C, Welsh-Bohmer K, et al. Cognitive function in late life depression: relationships to depression severity, cerebrovascular risk factors and processing speed. *J Biol Psychiatry* (2006) **60**:58–65. doi:10.1016/j.biopsych.2005.09.019
37. Nebes RD, Butters MA, Mulsant BH, Pollock BG, Zmuda MD, Houck PR, et al. Decreased working memory and processing speed mediate cognitive impairment in geriatric depression. *Psychol Med* (2000) **30**(3):679–91. doi:10.1017/S0033291799001968
38. Sexton CE, Allan CL, Le Mausurier M, Mc Dermott LM, Kalu UG, Herrmann LL, et al. Magnetic resonance imaging in late-life depression: multimodal examination of network disruption. *Arch Gen Psychiatry* (2012) **69**(7):680–9. doi:10.1001/archgenpsychiatry.2011.1862
39. Kok R, Verhey F. *Dutch Translation of the Mini Mental State Examination (Folstein et al., 1975)*. Altrecht: GGZ (2002).
40. Tombaugh TN. McIntyre. The mini-mental state examination: a comprehensive review. *J Am Geriatr Soc* (1992) **40**(9):922–35.
41. Anstey KJ, Burns RA, Birrell CL, Steel D, Kiely KM, Luszcz MA. Estimates of probable dementia prevalence from population-based surveys compared with dementia estimates based on meta-analyses. *BMC Neurol* (2010) **10**:62. doi:10.1186/1471-2377-10-62
42. World Medical Association. World Medical Association Declaration of Helsinki ethical principles for medical research involving human subjects. *JAMA* (2013) **310**(20):2191–4. doi:10.1001/jama.2013.281053
43. Yesavage JA, Brink T. Development and validation of a geriatric depression screening scale. A preliminary report. *J Psychiatr Res* (1982) **17**:37–49. doi:10.1016/0022-3956(82)90033-4
44. Spielberger CD, Gorsuch RL, Lushene PR, Vagg PR, Jacobs GA. *Test Manual for the State-Trait Anxiety Inventory*. Palo Alto, California: Consulting Psychologists Press, Inc (1983).
45. Weme de RJC, Hoeksema T, Goekoop JG. De Widlöcher remmingsschaal, een Nederlandse schaal voor het meten van psychomotore remming. *Acta Neuropsychiatr* (1996) **8**:56–63.
46. Van Hoof J, Hulstijn W, Van Mier H, Pagen M. Figure drawing and psychomotor retardation: preliminary report. *J Affect Disord* (1993) **29**:263–6. doi:10.1016/0165-0327(93)90016-D
47. Sabbe B, Hulstijn W, Van Hoof J, Tuynman Qua HG, Zitman F. Retardation in depression: assessment by means of simple motor tasks. *J Affect Disord* (1999) **55**:39–44. doi:10.1016/S0165-0327(98)00087-1
48. Maarse FJ, Janssen HJ, Dexel F. A special pen for an XY-tablet. In: Maarse FJ, Mulder LJM, Sjouw WPB, Akkerman AE, editors. *Computers in Psychology: Methods, Instrumentation and Psychodiagnostics*. Amsterdam: Swets Zeitlinger (1988). p. 133–9.
49. McLeod DR, Griffiths RR, Bigelow GE, Yingling J. An automated version of the digit symbol substitution test (DSST). *Behav Res Methods Instrum* (1982) **14**:463–6. doi:10.3758/BF03203313
50. Wechsler D. *Wechsler Adult Intelligence Scale–Revised*. San Antonio, TX: The Psychological Corporation (1981).
51. Wechsler D. *WAIS-III Administration and Scoring Manual*. San Antonio, TX: The Psychological Corporation (1997).
52. Psychological Assessment Resources. *Computerised Wisconsin Card Sort Task Version 4 (WCST)*. Lutz, Florida: Psychological Assessment Resources Inc. (2003).
53. Barceló F, Knight RT. Both random and perseverative errors underlie WCST deficits in prefrontal patients. *Neuropsychologia* (2002) **40**(3):349–56. doi:10.1016/S0028-3932(01)00110-5
54. Bardenhagen FJ, Bowden SC. Cognitive components in perseverative and nonperseverative errors on the object alternation task. *Brain Cogn* (1998) **37**(2):224–36. doi:10.1006/brcg.1997.0971
55. Greve KW, Bianchini KJ, Hartley SM, Adams D. The Wisconsin card sorting test in stroke rehabilitation: factor structure and relationship to outcome. *Arch Clin Neuropsychol* (1999) **14**(6):497–509. doi:10.1093/arclin/14.6.497
56. Greve KW, Bianchini KJ, Mathias CW, Houston RJ, Crouch JA. Detecting malingered performance with the Wisconsin card sorting test: a preliminary investigation in traumatic brain injury. *Clin Neuropsychol* (2002) **16**(2):179–91. doi:10.1076/clin.16.2.179.13241
57. Stroop J. Studies of interference in serial verbal reaction. *J Exp Psychol* (1935) **18**:643–62. doi:10.1037/h0054651
58. McLeod CM. Half a century of research on the Stroop effect: an integrative review. *Psychol Bull* (1991) **109**:163–202. doi:10.1037/0033-2909.109.2.163
59. Dodrill CB. A neuropsychological battery for epilepsy. *Epilepsia* (1978) **19**(6):611–23. doi:10.1111/j.1528-1157.1978.tb05041.x
60. Saan RJ, Deelman BG. *De 15-woordentest A en B (een voorlopige handleiding)*. Groningen: Afdeling Neuropsychologie AZG (1986).
61. Cohen J. A power primer. *Psychol Bull* (1992) **112**(1):155–9. doi:10.1037/0033-2909.112.1.155
62. Sabbe B, Hulstijn W, Van Hoof J, Zitman F. Retardation and antidepressant treatment: changes in fine motor retardation in depressed patients treated with fluoxetine. *J Affect Disord* (1999) **40**:149–57. doi:10.1016/0165-0327(96)00052-3
63. Pier MP. *Psychomotor Retardation in Subtypes of Depression*. Enschede: Printpartners Ipskamp (2006).
64. Destoop M. Multimodal perspectives on affective disorders. From clinics to imaging [Doctoral thesis]. Antwerpen: Universiteit Antwerpen, Faculteit geneeskunde en gezondheidswetenschappen (2013).
65. Smith PL, Ratcliff R. Psychology and neurobiology of simple decisions. *Trends Neurosci* (2004) **27**(3):161–8. doi:10.1016/j.tins.2004.01.006
66. Walther S, Hügli S, Höfle O, Federspiel A, Horn H, Bracht T, et al. Frontal white matter integrity is related to psychomotor retardation in major depression. *Neurobiol Dis* (2012) **47**:13–9. doi:10.1016/j.nbd.2012.03.019
67. Rypma B, Berger JS, Prabhakaram V, Bly BM, Kimberg DY, Biswal BB, et al. Neural correlates of cognitive efficiency. *J Neuroimage* (2006) **33**:969–79. doi:10.1016/j.neuroimage.2006.05.065
68. Bracht T, Federspiel A, Schnell S, Horn H, Höfle O, Wiest R, et al. Cortico-cortical white matter motor pathway microstructure is related to psychomotor retardation in major depressive disorder. *PLoS One* (2012) **7**(12):e52238. doi:10.1371/journal.pone.0052238
69. Zuromski CF, Rubin EH. *Psychiatry and Clinical Neuroscience: A Primer*. New York: Oxford University Press (2011).
70. Walther S, Höfle O, Federspiel A, Horn H, Hügli S, Wiest R, et al. Neural correlates of disbalanced motor control in major depression. *J Affect Disord* (2012) **136**:124–33. doi:10.1016/j.jad.2011.08.020
71. Dyck van CH, Avery RA, Mac Avoy MG, Marek KL, Quinlan DM, Baldwin RM, et al. Striatal dopamine transporters correlate with simple reaction time in elderly subjects. *Neurobiol Aging* (2008) **29**:1237–46. doi:10.1016/j.neurobiolaging.2007.02.012
72. Harper Mozley L, Gur RC, Mozley RD, Gur RE. Striatal dopamine transporters and cognitive functioning in healthy men and women. *Am J Psychiatry* (2001) **158**(9):1492–9. doi:10.1176/appi.ajp.158.9.1492
73. Wise RA. Dopamine, learning and motivation. *Nat Rev Neurosci* (2004) **5**:483–94. doi:10.1038/nrn1406
74. Treadway MT, Zald D. Reconsidering anhedonia in depression: lessons from translational neuroscience. *Neurosci Biobehav Rev* (2011) **35**(3):537–55. doi:10.1016/j.neubiorev.2010.06.006

75. Mingote S, Font L, Farrar AM, Vontell R, Worden LT, Stopper CM, et al. Nucleus accumbens adenosine A2A receptors regulate exertion of effort by acting on the ventral striatopallidal pathway. *J Neurosci* (2008) **28**(36):9037–46. doi:10.1523/JNEUROSCI.1525-08.2008
76. Morrens M, Hulstijn W, Sabbe B. Psychomotor slowing in schizophrenia. *Schizophr Bull* (2007) **33**(4):1038–53. doi:10.1093/schbul/sbl051
77. Moore AR, O'Keeffe ST. Drug-induced cognitive impairment in the elderly. *Drugs Aging* (1999) **15**(1):15–28. doi:10.2165/00002512-199915010-00002
78. Robles Bayón A, Gude Sampedro F. Prescripciones inconvenientes en el tratamiento del paciente con deterioro cognitivo [Inappropriate treatments for patients with cognitive decline]. *Neurologia* (2014) **29**(9):523–32 [Original article in Spanish]. doi:10.1016/j.nrleng.2012.05.009
79. Hickie IB, Naismith SL, Ward PB, Little CL, Pearson M, Scott EM, et al. Psychomotor slowing in older patients with major depression: relationships with blood flow in the caudate nucleus and white matter lesions. *Psychiatry Res* (2009) **155**(3):211–20. doi:10.1016/j.pscychresns.2007.01.006
80. Soumaré A, Elbaz A, Zhu Y, Maillard P, Crivello F, Tavernier B, et al. White matter lesions volume and motor performances in the elderly. *Ann Neurol* (2009) **65**(6):706–15. doi:10.1002/ana.21674
81. Rabbitt P, Scott M, Lunn M, Thacker N, Lowe C, Pendleton N, et al. White matter lesions account for all age-related declines in speed but not in intelligence. *Neuropsychology* (2007) **3**:363–70. doi:10.1037/0894-4105.21.3.363

Conflict of Interest Statement: This research was supported by a financial grant of Lundbeck.

Received: 01 October 2014; accepted: 19 December 2014; published online: 26 January 2015.
*Citation: Beheydt LL, Schrijvers D, Docx L, Bouckaert F, Hulstijn W and Sabbe B (2015) Psychomotor retardation in elderly untreated depressed patients. Front. Psychiatry **5**:196. doi: 10.3389/fpsyt.2014.00196*
This article was submitted to Schizophrenia, a section of the journal Frontiers in Psychiatry.

frontiers in PSYCHIATRY

ORIGINAL RESEARCH ARTICLE
published: 04 December 2014
doi: 10.3389/fpsyt.2014.00176

Functional and structural alterations in the cingulate motor area relate to decreased fronto-striatal coupling in major depressive disorder with psychomotor disturbances

Benny Liberg[1,2,3]*, Paul Klauser[1,4], Ian H. Harding[1,5], Mats Adler[2], Christoffer Rahm[1,6], Johan Lundberg[2], Thomas Masterman[2], Caroline Wachtler[7,8], Tomas Jonsson[3,9], Maria Kristoffersen-Wiberg[3,10], Christos Pantelis[1] and Björn Wahlund[11]

[1] *Department of Psychiatry, Melbourne Neuropsychiatry Centre, The University of Melbourne, Melbourne, VIC, Australia*
[2] *Section of Psychiatry, Department of Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden*
[3] *Department of Clinical Science, Intervention and Technology (CLINTEC), Division of Medical Imaging and Technology, Karolinska Institutet, Stockholm, Sweden*
[4] *Monash Clinical and Imaging Neuroscience, School of Psychology and Psychiatry, Monash University, Clayton, VIC, Australia*
[5] *School of Psychological Sciences, Monash University, Melbourne, VIC, Australia*
[6] *Department of Medicine Huddinge, Karolinska Institutet, Stockholm, Sweden*
[7] *Primary Care Research Unit, Department of General Practice, The University of Melbourne, Melbourne, VIC, Australia*
[8] *Centre for Family Medicine (CeFAM), Department of Neurobiology, Care Sciences and Society, Karolinska Institutet, Stockholm, Sweden*
[9] *Department of Medical Physics, Karolinska University Hospital Huddinge, Stockholm, Sweden*
[10] *Department of Radiology, Karolinska University Hospital, Stockholm, Sweden*
[11] *Department of Energy and Engineering, Swedish University of Agricultural Sciences, Uppsala, Sweden*

Edited by:
Sebastian Walther, University of Bern, Switzerland

Reviewed by:
Andrea Federspiel, University of Bern, Switzerland
Didier Schrijvers, University of Antwerp, Belgium

****Correspondence:***
Benny Liberg, Department of Psychiatry, Melbourne Neuropsychiatry Centre, Alan Gilbert Building, Level 3, 161 Barry Street, Carlton South, VIC 3053, Australia
e-mail: benny.liberg@gmail.com

Psychomotor disturbances are a classic feature of major depressive disorders. These can manifest as lack of facial expressions and decreased speech production, reduced body posture and mobility, and slowed voluntary movement. The neural correlates of psychomotor disturbances in depression are poorly understood but it has been suggested that outputs from the cingulate motor area (CMA) to striatal motor regions, including the putamen, could be involved. We used functional and structural magnetic resonance imaging to conduct a region-of-interest analysis to test the hypotheses that neural activation patterns related to motor production and gray matter volumes in the CMA would be different between depressed subjects displaying psychomotor disturbances ($n = 13$) and matched healthy controls ($n = 13$). In addition, we conducted a psychophysiological interaction analysis to assess the functional coupling related to self-paced finger-tapping between the caudal CMA and the posterior putamen in patients compared to controls. We found a cluster of increased neural activation, adjacent to a cluster of decreased gray matter volume in the caudal CMA in patients compared to controls. The functional coupling between the left caudal CMA and the left putamen during finger-tapping task performance was additionally decreased in patients compared to controls. In addition, the strength of the functional coupling between the left caudal CMA and the left putamen was negatively correlated with the severity of psychomotor disturbances in the patient group. In conclusion, we found converging evidence for involvement of the caudal CMA and putamen in the generation of psychomotor disturbances in depression.

Keywords: major depression, bipolar disorder, psychomotor disturbances, cingulate cortex, cingulate motor area, striatum, putamen

INTRODUCTION

Psychomotor disturbance is a cardinal feature of major depressive disorder. The severity of psychomotor disruption is clinically associated with depression severity and predicts response to certain pharmacological treatments (1–4). Psychomotor disturbances transcend illness phase and manifest as changes in interactiveness and spontaneity, alongside reductions in facial expression, body mobility, postural tone, speed of movement, and speech (5–7). Investigations of the neural correlates underpinning psychomotor disturbances remain sparse; indeed, the motor system has been relatively neglected in brain imaging studies of psychiatric disorders in general (8). However, available evidence points to metabolic deficits, neurochemical changes, and altered structural connections and functional connectivity involving large-scale brain networks that connect frontal cortical regions and subcortical (esp. basal ganglia) areas (9–24). Interactions between the striatum, frontal motor regions, and prefrontal association cortices are known to be critical to the initiation and regulation of motor output and cognitive processing (25, 26). However, the localization and relevance of brain abnormalities in these fronto-striatal systems to psychomotor disturbances observed in depression remains largely unknown.

One important target for investigation of psychomotor disturbances is the cingulate cortex. Converging evidence supporting the involvement of the cingulate cortex in the clinical expression of major depressive disorder comes through experimental studies using interventions, such as sadness induction (27), cognitive behavioral therapy (28), pharmacological probes, such as antidepressants and dopamine-modulating treatments (29, 30), or neuromodulation such as electroconvulsive therapy or transcranial magnetic stimulation (31–35). Additionally, secondary cingulate cortex lesions can also lead to a neuropsychiatric condition known as akinetic mutism that involves severe alterations of volition, psychomotor slowing, and apathy – clinical features that resemble severe major depressive disorder (36, 37).

The cingulate cortex has been suggested to integrate volition, affect, and behavior. It is located on the midline rim of the corpus callosum and is generally divided anatomically into four distinct subregions (38, 39). One of these subregions is the midcingulate region, which contains the cingulate motor area (CMA) (40, 41). The CMA is a cortical midline structure, located in the posterior frontal lobe, superior to the corpus callosum, and inferior to the supplementary motor area. The CMA has been implicated in motor behaviors with affective incentives (42) and receives neural signals from affective limbic regions, frontal executive regions, and motor regions (37, 43). A caudal subregion of the CMA has long been implicated in the execution of simple motor tasks, but only recently has its somatotopy and functional organization been determined with more spatially precise brain imaging (44–47). Functional connectivity and retrograde tracings in primates suggest inputs from caudal CMA to lateral putamen in general, and to rostral ventral putamen in particular, overlap with inputs from primary motor areas (48, 49).

There is currently no empirically validated functional anatomical model of psychomotor disturbances in major depressive disorder. However, within the anatomical framework of large-scale brain networks, Vogt proposed one such pathophysiological model in which a loss of neurons in the cortical output layer (layer V) of the cingulate cortex specifically attenuates the output from the CMA to subcortical motor regions, resulting in a paucity of internally guided movement and speech (50). Clinically, this neural disruption could be reflected in the altered response to external events and slowed movements that characterize psychomotor disturbances observed in major depressive disorder.

Using the framework of Vogt's theory of movement paucity in major depressive disorder, we hypothesized that psychomotor disturbances in major depressive disorder rely on structural and functional abnormalities in a network encompassing the CMA and striatal motor regions. We predict that participants with major depressive disorder show modifications of functional activation in left CMA and left posterior putamen during a task involving the generation of rapid right-lateralized finger movements (i.e., self-paced finger-tapping). We also anticipate that these functional alterations are accompanied by modifications of gray matter volume in both the left CMA and left putamen. Finally, the severity of both functional and structural abnormalities is predicted to correlate with the degree of observed psychomotor disturbances.

MATERIALS AND METHODS

STUDY SAMPLE

The Karolinska University Hospital and Stockholm City Council Ethics Committee approved the study protocol. Each subject gave oral and written informed consent to participate in this study. Thirteen patients with a bipolar I diagnosis ($n = 9$), bipolar II diagnosis ($n = 1$), or unipolar depression diagnosis ($n = 3$) were recruited from The Affective Disorders Unit at Psychiatry Southwest at Karolinska University Hospital in Huddinge, Sweden. All patients were experiencing a current episode of depression with a duration > 1 month and featuring psychomotor disturbances. No patient fulfilled the diagnostic criteria for concurrent mania, hypomania, or rapid cycling disorder. Thirteen healthy controls without psychiatric diagnoses were recruited. Clinical diagnoses were confirmed using a computerized version of the Structured Clinical Interview for DSM Disorders (51). All participants were right handed, had no history of neurologic illness, and had normal or corrected-to-normal visual acuity (52). All patients were on medication (**Table 1**), and all controls were drug free.

Table 1 | Sample characteristics.

Variable	Controls	Patients
Sex	6 F, 7 M; $n = 13$	9 F, 4 M; $n = 13$
Age (years)	39 (29–67)	44 (24–62)
Bipolar depression (type I, type II)		$n = 10$ ($n = 9$, $n = 1$)
Unipolar depression (recurrent, first episode)		$n = 3$ ($n = 2$, $n = 1$)
MADRS total score		28.9 (11–48)
CORE total score		17.7 (10–36)
CORE retardation items score		9.1 (3–15)
AS-18 retardation factor score		8.2 (0–12)
AS-18 depression factor score		23.2 (1–36)
AS-18 mania factor score		4.9 (0–13)
AS-18 total score		36.2 (2–58)
Lithium		$n = 4$
Typical neuroleptics (FGA)		$n = 2$
Atypical neuroleptics (SGA)		$n = 4$
Anticonvulsants		$n = 5$
Antidepressant (TCA)		$n = 1$
Antidepressant (SSRI)		$n = 1$
Antidepressant (SNRI)		$n = 5$
MAO-I		$n = 1$
Thyroxine		$n = 1$
Electroconvulsive treatment		$n = 2$

If not otherwise specified, values represent the mean and the range is given into brackets.

M/F, male/female; FGA, first-generation antipsychotics; SGA, second-generation antipsychotics; TCA, tricyclic antidepressants; SSRI, serotonin reuptake inhibitors; SNRI, serotonin-noradrenalin reuptake inhibitors; MAO-I, monoamine-oxidase inhibitors.

Depression severity was rated by Benny Liberg and Mats Adler with the Montgomery Åsberg Depression Rating Scale (53) and psychomotor disturbance was rated with the CORE scale (54). Retrospective assessment of patient files did not reveal the presence of extrapyramidal symptoms or signs in medicated patients.

Image acquisition

Participants performed finger-tapping while in the MRI-scanner, following instructions on a computer screen viewed through a head-coil mounted mirror. Before the experiment started, participants were shown how to perform finger-tapping, defined as a thumb-index finger opposition of the right hand. Participants were asked to tap as quickly as possible. The experiment had an ON/OFF design consisting of 20 s of finger-tapping followed by 20 s of rest. During the first second of each ON-period, the instruction "tap" was presented, and the screen then turned black for 19 s. Rest periods were indicated by a fixation-cross presented for 20 s. This stimulus cycle was repeated seven times. The total functional scanning time was 280 s.

A Siemens Avanto 1.5-T scanner was used to acquire blood oxygen level dependent (BOLD) sensitive T2*-weighted echo planar images. Each echo planar image comprised 22 axial slices with a resolution of 3.75 mm × 3.75 mm × 5 mm and an interslice interval of 1 mm. Volumes were acquired with a repetition time (TR) of 2.5 s, an echo time (TE) of 30 ms, a field-of-view of 64 mm × 64 mm, and a flip angle of 90°. The first six (dummy) volumes of each run were discarded to allow for T1 equilibration effects. A total of 112 volumes were acquired. After the functional scans had been collected, a T1-weighted anatomical image [magnetization prepared rapid acquisition gradient echo (MP-RAGE)], 128 slices; TR, 2400 ms; TE, 3.44 ms; with a voxel size of 1.3 mm × 1.3 mm × 1.3 mm] was acquired for all subjects. To rule out radiological signs of pathology, a consultant in neuroradiology (Maria Kristoffersen-Wiberg) assessed the anatomical scans of each subject.

Region-of-interest masks

We used the software GingerALE 2.3 to define the left caudal CMA mask. GingerALE allows for meta-analysis of human brain imaging studies using published co-ordinates in standard space (55). Co-ordinates were derived from a study that mapped the functional anatomy of the CMA at the single-subject level (44). Input foci data included co-ordinates in the left hemisphere that represented neural activation in the CMA during motor execution using the right hand. Significant clusters in the whole-brain analysis were determined by a (corrected using a Monte-Carlo approach) cluster significance threshold of $p \leq 0.05$. The resulting ROI mask is illustrated in **Figure 3**. The ROI mask for the putamen region connecting to the caudal motor cortex was derived from the Oxford Imanova Striatal Connectivity Atlas (seven-regions) supplied with FSL (56).

Analysis of functional activations

Imaging data were analyzed using the FSL 5.0.2 software suite [The Oxford Centre for Functional MRI of the Brain (FMRIB), Oxford University, United Kingdom]. Data processing was carried out using the fMRI Expert Analysis Tool version 5.98. Rigid-body head motion correction was first performed (57). We subsequently de-noised the data using the multivariate ICA-based classifier FIX (58, 59), based on a conservative threshold of five components. Non-brain tissue was then removed (60) and the functional data were smoothed using a Gaussian kernel set to a full-width half-maximum (FWHM) of 6 mm. To account for time differences in slice acquisition, we performed slice-timing correction using Fourier-space time series phase shifting. In addition, we normalized the grand-mean intensity of the entire four-dimensional (4D) dataset by a single multiplicative factor and filtered out physiological noise using a high-pass temporal filter set to a period of 100 s. Registration of the data to standard anatomical space was undertaken with the high-resolution structural (T1) scan using boundary-based registration with BBR, and affine linear registration with FLIRT (61). Estimated transformations were subsequently applied to the co-registered functional data. The time series of each subject was modeled using a general linear model (GLM) containing a single predictor representing the on–off time-course of the experiment, convolved with a hemodynamic response function (gamma). Parameter estimates (PEs) were calculated for all brain voxels. Correction for local autocorrelation in the time series was undertaken using FILM (62).

The subject-specific contrast (COPE) images of the finger-tapping effect were then entered into a second-level group analysis. As our patient sample had a different sex distribution than our control group, we added age and sex as covariates in the regression model to remove their potential confounding effects. We also created a 4D covariate image of gray matter using the feat_gm_prepare script. The 4D image output containing gray matter partial volume information was inserted as voxel-dependent EVs in the GLM model for each subject (63). The higher level analysis was carried out using FMRIB's local analysis of mixed effects stage 1 and stage 2 (64–66). Z (Gaussianized T/F) statistic images in the ROI analysis were thresholded using clusters determined by $Z \geq 2.3$ and a (corrected using Gaussian random field theory) cluster significance threshold of $p \leq 0.05$.

Analysis of functional connectivity

We performed a psychophysiological interaction (PPI) analysis to determine group differences in task-dependent alterations of functional coupling between the left caudal CMA and left putamen regions connected to caudal cortical motor regions. Analysis was performed in SPM8 using the preprocessed first-level data described above (preprocessed in FSL). A PPI analysis determines how the statistical dependency between the time courses of neural activation in a region-of-interest (ROI) and a targeted brain region depends on a task context (67). We extracted the BOLD time series data from each subject within a 5 mm sphere centered at the peak of the task-related group activation difference within the left CMA (see Results). At the first level of analysis, a GLM consisting of three predictors was specified: the left CMA time series data as a physiological regressor, the task-based model as psychological regressor, and the interaction term (the PPI) formed by their crossproduct. We entered first-level COPE images representing the interaction term into a second-level random effects analysis of group differences in a region of the left putamen connected to caudal cortical motor areas involved in movement. Inference was undertaken

using two-sample T-tests restricted to a mask of the left putamen and corrected for multiple comparisons ($p \leq 0.05$) based on minimum cluster-extent thresholds estimated using the AlphaSim permutation procedure (REST toolbox; http://pub.restfmri.net). Simulations were run using an uncorrected voxel-level threshold of $p \leq 0.05$, across 1000 permutations, resulting in a minimum required cluster-threshold of 14 voxels ($p \leq 0.05$, corrected at the mask level).

Analysis of gray matter volume

Paul Klauser and Benny Liberg inspected every image to assess the presence of artifacts or gross anatomical abnormalities that could impact image preprocessing. We estimated gray matter volume using voxel-based morphometry (VBM) implemented in SPM8 (http://www.fil.ion.ucl.ac.uk/spm/software/spm8/). Each participant's T1-weighted anatomical scan was segmented into gray, white, and cerebrospinal fluid compartments using the VBM8 toolbox (http://dbm.neuro.uni-jena.de/vbm) set to default parameters. Native-space gray matter images were then spatially normalized to the DARTEL template in MNI standard space created from 550 healthy control subjects from the IXI-database (http://www.brain-development.org). For the generation of gray matter volumes, Jacobian determinants were used to modulate gray voxel intensities with non-linear warping only in order to preserve original gray matter volumes while discarding initial differences in brain sizes. The images were then smoothed with a 6 mm full-width-half-maximum Gaussian kernel prior to statistical analysis. A GLM was used to test for group differences in gray matter volume at each voxel within the CMA ROI mask, as implemented in Randomise (http://fsl.fmrib.ox.ac.uk/fsl/randomise). All results were corrected for multiple comparison type I error at the ROI mask level using a non-parametric cluster size-based procedure. We set the voxelwise cluster-forming threshold to $T \geq 2.5$. Then, a clusterwise p-value corrected at the ROI level was calculated from a permutation test (10,000 permutations). Age and gender were entered as covariates in the GLM.

Correlation analyses

Calculation of Spearman's Rho correlation coefficients between CORE ratings, imaging metrics, and neurobiological indices were assessed to determine associations between clinical phenomenology and brain abnormalities determined with different imaging modalities.

RESULTS

FUNCTIONAL ACTIVATION

In our group, comparison of task-related neural activation in the caudal CMA during self-paced finger-tapping, we found that patients activated the left caudal CMA more than healthy controls (cluster size: 356 voxels/2848 mm^3; $Z_{CMA} = 3.01$; $p = 0.003$, corrected at the cluster level; peak voxel: $x = -6$, $y = -10$, $z = 38$; **Figure 1**; **Table 2**).

FUNCTIONAL CONNECTIVITY

In our PPI analysis of task-related functional coupling between the caudal CMA and the posterior putamen regions connected to caudal motor regions in the frontal lobe, we found significant group differences (cluster size: 31 voxels/248 mm^3, $p = 0.02$, corrected; peak voxel: $x = -26$, $y = -6$, $z = 0$; **Figure 1**). We found that neural activation in controls showed a task-related correspondence between the left caudal CMA and left posterior putamen regions connected to caudal motor regions in the frontal lobe, whereas this relationship was absent in the patients.

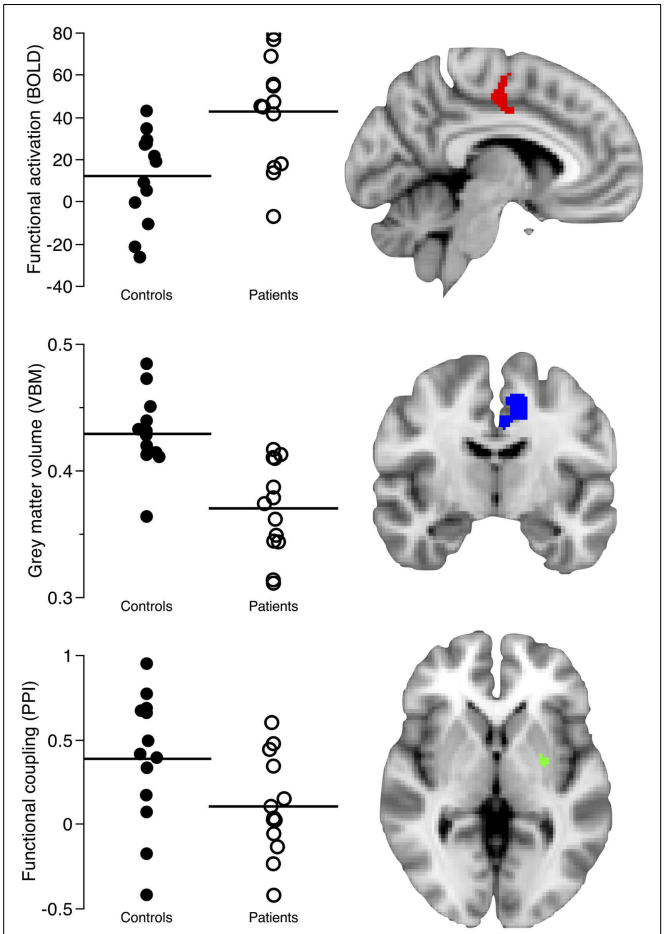


FIGURE 1 | The image shows the structural and functional imaging findings in the left caudal cingulate motor area (CMA) and putamen regions connected to caudal motor regions in the frontal lobe. The first row shows the contrast parameter estimates reflecting how patients activate the caudal cingulate motor regions more than healthy controls ($Z > 2.3$, $p = 0.05$, corrected) during self-paced finger-tapping. The second row shows decreased gray matter volume in the left CMA of patients ($T > 2.5$, $p = 0.05$, corrected). The third row shows the decreased functional coupling of the left CMA and left posterior putamen regions connected to caudal motor regions in the frontal lobe during self-paced finger-tapping ($p = 0.02$, corrected). Metrics (mean) from clusters of between-group differences in the left caudal CMA and posterior putamen were retrieved using masks comprising 356 voxels/2848 mm^3 from the functional magnetic resonance imaging analysis, 941 voxels/3176 mm^3 from the voxel-based morphometry analysis, and 31 voxels/248 mm^3 from the psychophysiological interaction analysis.

GRAY MATTER VOLUME

In our comparison of left CMA gray matter volume in patients and controls, we observed one cluster of decreased gray matter volume

Table 2 | Functional activation statistics during self-paced finger-tapping (patient > controls).

Z-max	Cluster	MNI co-ordinates			Anatomical label
		x	*y*	*z*	
3.85	1	2	−14	52	38% precentral gyrus, 36% SMA
3.66		−2	−14	50	38% SMA, 34% precentral gyrus
3.01		−6	−10	38	32% cingulate gyrus, anterior division (CMA)
2.75		4	−2	52	73% SMA
2.53		8	−2	48	49% SMA

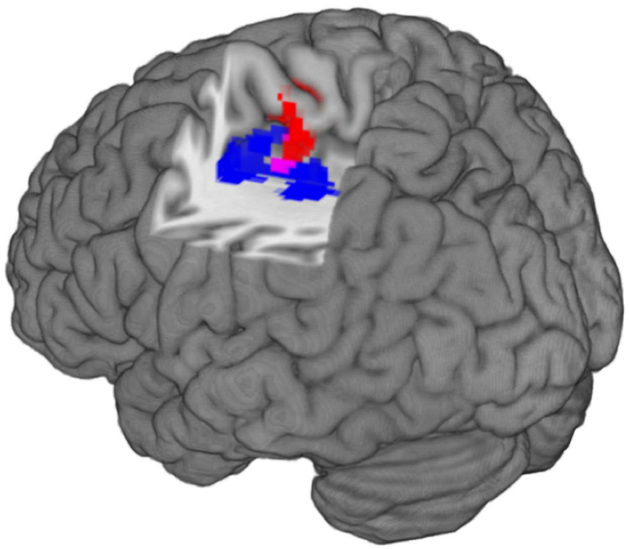


FIGURE 2 | The image shows the localization of structural and functional imaging findings in the left caudal cingulate motor. Left is left in the image. The red cluster represents increased functional activation in patients compared to controls ($Z > 2.3$, $p = 0.05$, corrected). The blue cluster represents gray matter volume decreases in patients compared to controls ($T > 2.5$, $p = 0.05$, corrected). The purple voxels represent the overlap between function and structural findings.

in the patient group that encompassed the left caudal CMA (cluster size: 941 voxels/3176 mm^3; $T_{CMA} = 6.79$; $p = 0.01$, corrected at the cluster level; peak voxel: $x = -9$, $y = 4.5$, $z = 33$; **Figures 1** and **2**).

CROSS-MODALITY RELATIONSHIPS

We found a statistically significant and negative correlation (rho: −0.57, $p = 0.002$; **Table 3**) between mean functional activation (356 voxels/2848 mm^3) and gray matter volume (941 voxels/3176 mm^3) in the left caudal CMA across both groups. There was also a statistically significant and positive correlation (rho: 0.52, $p = 0.006$, **Table 3**) between gray matter volume (941 voxels/3176 mm^3) and functional coupling of the left caudal CMA and left posterior putamen regions connected to caudal motor regions in the frontal lobe (31 voxels/248 mm^3) across both groups. The spatial overlap of between-group differences in gray matter volume and functional activation is shown in **Figure 2**.

Table 3 | Non-parametric correlations between neuroimaging modalities and clinical ratings.

Variables	Size	#Voxels (mm^3)	Rho	*p*
Functional activation – CORE (patients)	$n = 13$	356 (2848)	0.28	0.35
Functional coupling – CORE (patients)	$n = 13$	31 (248)	−0.57	0.04
Gray matter volume – CORE (patients)	$n = 13$	941 (3176)	−0.11	0.71
Gray matter volume – Functional activation	$n = 26$	941 (3176)/356 (2848)	−0.57	0.002
Gray matter volume – Functional coupling	$n = 26$	941 (3176)/31 (248)	0.52	0.006

CLINICAL CORRELATIONS

We found a statistically significant and negative correlation (rho = −0.57; $p = 0.04$, **Table 3**) between clinical ratings of psychomotor disturbances (CORE) in patients and functional coupling of the left caudal CMA and left posterior putamen regions connected to caudal motor regions in the frontal lobe (356 voxels/2848 mm^3). We did not find a significant correlation (rho = 0.39; $p = 0.18$) between CORE ratings and functional activation of the left caudal CMA (356 voxels/2848 mm^3) or between CORE ratings and gray matter volume in the left caudal CMA (rho = −0.11; $p = 0.71$; 941 voxels/3176 mm^3).

DISCUSSION

In the present study, we used structural and functional neuroimaging to investigate the contribution of the CMA to psychomotor disturbances in major depressive disorder. By combining neuroimaging modalities, we found converging evidence supporting a neural model of psychomotor disturbances that involves a fronto-striatal network contributing to motor execution. Specifically, we found that (1) patients activated the CMA more than healthy controls during right-handed self-paced finger-tapping; (2) functional coupling of the CMA and putamen was absent in patients compared to controls during task performance; (3) patients had decreased gray matter volume in the CMA; (4) clinical ratings of psychomotor disturbance in patients were negatively correlated with functional coupling of the CMA and putamen; and (5) gray matter volume of the CMA region with between-group differences was negatively correlated with functional activation, and positively correlated with functional coupling.

Our study lends experimental support to the involvement of a fronto-striatal network in the emergence of psychomotor disturbances in major depressive disorder. In our study, gray matter volume decreases were associated with decreased functional coupling of the left caudal CMA and left posterior putamen during motor execution of a right-handed self-paced finger-tapping task. The midcingulate region comprising the CMA is known to provide extensive output to skeletomotor areas, including the striatum (41). Changes in the CMA would, therefore, impact upon its

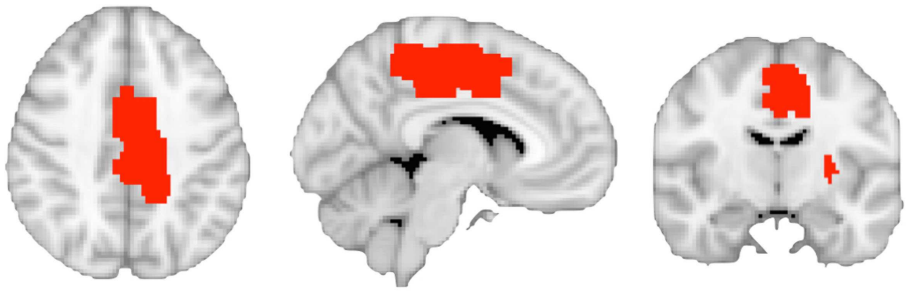


FIGURE 3 | The image shows the binarized region of interest masks defining the left caudal cingulate motor area and the left putamen regions connected to caudal motor regions in the frontal lobe.

glutamatergic inputs to subcortical motor systems and, in turn, lead to impairments in motor behavior, i.e., psychomotor disturbances. Although beyond the scope of the current study, this finding may be relevant to neuron loss in cortical layer V, from which efferent fibers are derived, in accordance with Vogt's model of motor dysfunction (50).

It is interesting to note the relative position of the clusters resulting from the functional and the structural analysis: few voxels show an overlap between the functional cluster representing increased neural activity and the structural cluster representing decreased gray matter volume in the CMA of patients (**Figure 2**). The interpretation of the spatial extent of clusters, resulting from cluster-based statistics is known to be problematic, especially when relatively low cluster-forming thresholds are used like in this study (i.e., $T > 2.5$) (68). Nevertheless, the increase of functional activation in an area that seems to be spared by gray matter volume loss may represent a less affected region or a compensatory mechanism. Compensatory cortical plasticity has been previously described after acute brain lesions but a similar mechanism could also be involved following more chronic alterations of brain networks in the context of mental illness (69).

This study conforms to previous studies that have shown paralimbic hyperactivation in major depressive disorder using both molecular metabolic imaging and functional magnetic resonance imaging with BOLD (70, 71). Hypothetically, a loss of neurons in cingulate layer V suggested by Vogt et al. (50) could arise from excess glutamate signaling with impaired plasticity and neural resilience (72). However, the BOLD signal comprises several neuronal and vascular factors that preclude a specific association of increased activation and hyperglutamatergia (73). Indirect correlational evidence for cingulate hyperglutamatergia may be inferred from the positive correlation of glutamate signaling and spontaneous neural activity of paralimbic medial frontal and posterior cingulate regions: the so-called "default-mode" network (74, 75). Several studies suggest that this network is hyperactivated in major depressive disorder (76–78). In a previous study of the bipolar disorder subgroup of this sample ($n = 9$), there was an increased activation among depressed patients in the default-mode network during motor execution (15). However, the opposite association between glutamate, functional connectivity, and depression severity has also been shown (79). Thus, we remain cautious regarding definitive interpretations of our findings in the context of the pathophysiology underlying psychomotor disturbances in major depressive disorder.

Our study has limitations. First, this is a ROI study where we had an *a priori* hypothesis involving selected brain regions in the left hemisphere known to activate during simple right-hand movements. The disadvantage of the ROI approach is that it discerns a comprehensive observation of the full large-scale neuronal networks implicated in these disturbances (80). However, our motivation for choosing the ROI approach was that our hypothesis addressed specific ideas based on previous research on the CMA in major depressive disorder. An advantage of the ROI approach is that it potentially increases the sensitivity of the neuroimaging methods we applied, and previous research suggests that ROI analyses may provide a better statistical control of both type I and type II errors than in whole-brain analyses as the ROI approach is less dependent on correction for multiple comparisons (81). This becomes even more important in smaller samples such as ours. Second, our brain imaging approach is restricted to inference from indirect monitoring of the disease underlying major depressive disorder. Functional imaging studies and anatomical mapping advocate a limbic hyperactivation in major depressive disorder and suggest that more anterior cingulate cortex regions convey limbic signals to the CMA, which in turn suggests that our observed CMA alterations may only be a tertiary marker for a disease that alters upstream nodes in the same neural network (29, 43). The BOLD contrast mechanism itself also highlights the importance of inputs to CMA (82). Third, the CMA and putamen are both rich in ascending midbrain dopamine afferents that contribute to the initiation, preparation, execution, and control of movement (56, 83). Six patients in our sample were treated with antipsychotic medication that affects dopamine transmission in both regions. This could potentially lead to misrepresentative and biased results. However, neuroimaging metrics in these six individuals were distributed across the whole patient sample, and there were no outliers in the patient group with respect to functional activation, gray matter volume, or functional coupling. Fourth, there are many types of motor behavior, and it is possible that finger-tapping does not engage identical fronto-striatal networks in the same way as more elaborate motor behavior. The strength of the finger-tapping task is that it is sensitive to pathology in fronto-striatal neurocircuitry and is considered to measure a defined entity: motor speed (84). Fifth, the BOLD signal in the

CMA may be subject to noise due to partial volume effects because of the spatial resolution of our functional scans. This contributes to a possible source of error in our PPI analysis. Finally, given the small sample size of our groups, the GLM may not provide the best fit of our second-level data. However, we analyzed our data at second level using a mixed effects analysis (FMRIB's Local Analysis of Mixed Effects stage 1 and stage 2) similar to a vast majority of comparable functional imaging studies. In order to confirm the validity of our results, we also re-analyzed data at second level with Randomise for non-parametric inference while using an identical statistical threshold. The spatial extent of those statistically significant results was close to identical regarding the CMA cluster of between-group differences. We would like to reiterate that even if the GLM does not provide the best fit for our second level analysis, the corrected *p*-value calculated by Randomise is valid, regardless the distribution of our data.

CONCLUSION

Our data are cross-sectional but implicates the possibility of a chain of events where primary neural hyperactivation in paralimbic regions has secondary effects on gray matter volume in fronto-striatal networks involved in movement. In our study, functional activation was negatively correlated with gray matter volume, which suggests an association between paralimbic hyperactivation and gray matter alterations. The positive correlation between gray matter volume and functional coupling supports the notion of diminished cortical output via layer V to subcortical regions that are involved in motor control. The functional coupling was also negatively correlated with clinical ratings, which suggests a role of decreased functional connectivity within fronto-striatal networks in the emergence of clinical psychomotor disturbances in major depressive disorder. Thus, our results propose an involvement of the CMA in the generation of psychomotor disturbances in a major depressive disorder. Our data also suggest the possibility of elucidating the causality of these events by using an experimental longitudinal study design and analyses of directional effective connectivity within these networks during motor performance.

AUTHOR CONTRIBUTIONS

All authors made substantial contributions to the conception and design of this work. Benny Liberg and Mats Adler collected the original data. Benny Liberg, Paul Klauser, and Ian H. Harding performed the analyses. All authors contributed to the interpretation of data for this work. Benny Liberg, Paul Klauser, and Ian H. Harding drafted the manuscript, which all authors critically revised for important intellectual content. All authors approved the final version of the manuscript. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

ACKNOWLEDGMENTS

We thank Kerstin Eriksson at the MRI Unit, Radiology Clinic, Karolinska University Hospital Huddinge for clinical assistance during scanning. We thank Andrew Zalesky for valuable comments on methodology. We also thank staff members of the Section of Affective Disorders, the Southwest Psychiatric Clinic (PSSV), Stockholm County Council, for assistance with recruiting patients. Benny Liberg received funding from Svenska Läkaresällskapet (The Swedish Society of Medicine, SLS-403101), the Southwest Psychiatric Clinic (PSSV), Stockholm County Council, and the Strategic Research Committee, Karolinska Institutet/Stockholm County Council, Sweden. Paul Klauser was supported by the Swiss National Science Foundation and the Swiss Society for Medicine and Biology Scholarships (ID: 148384). Professor Christos Pantelis was supported by a NHMRC Senior Principal Research Fellowship, Australia (ID: 628386).

REFERENCES

1. Buyukdura JS, McClintock SM, Croarkin PE. Psychomotor retardation in depression: biological underpinnings, measurement, and treatment. *Prog Neuropsychopharmacol Biol Psychiatry* (2011) **35**(2):395–409. doi:10.1016/j.pnpbp.2010.10.019
2. Schrijvers D, Hulstijn W, Sabbe BG. Psychomotor symptoms in depression: a diagnostic, pathophysiological and therapeutic tool. *J Affect Disord* (2008) **109**(1–2):1–20. doi:10.1016/j.jad.2007.10.019
3. Sobin C, Mayer L, Endicott J. The motor agitation and retardation scale: a scale for the assessment of motor abnormalities in depressed patients. *J Neuropsychiatry Clin Neurosci* (1998) **10**(1):85–92.
4. Sobin C, Sackeim HA. Psychomotor symptoms of depression. *Am J Psychiatry* (1997) **154**(1):4–17.
5. Berk M, Dodd S, Kauer-Sant'anna M, Malhi GS, Bourin M, Kapczinski F, et al. Dopamine dysregulation syndrome: implications for a dopamine hypothesis of bipolar disorder. *Acta Psychiatr Scand Suppl* (2007) (434):41–9. doi:10.1111/j.1600-0447.2007.01058.x
6. Malhi GS, Berk M. Does dopamine dysfunction drive depression? *Acta Psychiatr Scand Suppl* (2007) (433):116–24. doi:10.1111/j.1600-0447.2007.00969.x
7. Parker G, Hadzi-Pavlovic D, Brodaty H, Boyce P, Mitchell P, Wilhelm K, et al. Psychomotor disturbance in depression: defining the constructs. *J Affect Disord* (1993) **27**(4):255–65. doi:10.1016/0165-0327(93)90049-P
8. Kupferschmidt DA, Zakzanis KK. Toward a functional neuroanatomical signature of bipolar disorder: quantitative evidence from the neuroimaging literature. *Psychiatry Res* (2011) **193**(2):71–9. doi:10.1016/j.pscychresns.2011.02.011
9. Bracht T, Federspiel A, Schnell S, Horn H, Hofle O, Wiest R, et al. Cortico-cortical white matter motor pathway microstructure is related to psychomotor retardation in major depressive disorder. *PLoS One* (2012) **7**(12):e52238. doi:10.1371/journal.pone.0052238
10. Caligiuri MP, Brown GG, Meloy MJ, Eberson SC, Kindermann SS, Frank LR, et al. An fMRI study of affective state and medication on cortical and subcortical brain regions during motor performance in bipolar disorder. *Psychiatry Res* (2003) **123**(3):171–82. doi:10.1016/S0925-4927(03)00075-1
11. Lohr JB, Caligiuri MP. Abnormalities in motor physiology in bipolar disorder. *J Neuropsychiatry Clin Neurosci* (2006) **18**(3):342–9. doi:10.1176/appi.neuropsych.18.3.342
12. Exner C, Lange C, Irle E. Impaired implicit learning and reduced pre-supplementary motor cortex size in early-onset major depression with melancholic features. *J Affect Disord* (2009) **119**(1–3):156–62. doi:10.1016/j.jad.2009.03.015
13. Hickie IB, Naismith SL, Ward PB, Little CL, Pearson M, Scott EM, et al. Psychomotor slowing in older patients with major depression: relationships with blood flow in the caudate nucleus and white matter lesions. *Psychiatry Res* (2007) **155**(3):211–20. doi:10.1016/j.pscychresns.2007.01.006
14. Liberg B, Adler M, Jonsson T, Landen M, Rahm C, Wahlund LO, et al. The neural correlates of self-paced finger tapping in bipolar depression with motor retardation. *Acta Neuropsychiatr* (2013) **25**(1):43–51. doi:10.1111/j.1601-5215.2012.00659.x
15. Liberg B, Adler M, Jonsson T, Landen M, Rahm C, Wahlund LO, et al. Motor imagery in bipolar depression with slowed movement. *J Nerv Ment Dis* (2013) **201**(10):885–93. doi:10.1097/NMD.0b013e3182a5c2a7
16. Marchand WR, Lee JN, Suchy Y, Johnson S, Thatcher J, Gale P. Aberrant functional connectivity of cortico-basal ganglia circuits in major depression. *Neurosci Lett* (2012) **514**(1):86–90. doi:10.1016/j.neulet.2012.02.063

17. Marchand WR, Lee JN, Thatcher GW, Jensen C, Stewart D, Dilda V, et al. A functional MRI study of a paced motor activation task to evaluate frontal-subcortical circuit function in bipolar depression. *Psychiatry Res* (2007) **155**(3):221–30. doi:10.1016/j.pscychresns.2007.03.003
18. Marchand WR, Lee JN, Thatcher J, Thatcher GW, Jensen C, Starr J. A preliminary longitudinal fMRI study of frontal-subcortical circuits in bipolar disorder using a paced motor activation paradigm. *J Affect Disord* (2007) **103**(1–3):237–41. doi:10.1016/j.jad.2007.01.008
19. Walther S, Hugli S, Hofle O, Federspiel A, Horn H, Bracht T, et al. Frontal white matter integrity is related to psychomotor retardation in major depression. *Neurobiol Dis* (2012) **47**(1):13–9. doi:10.1016/j.nbd.2012.03.019
20. Bench CJ, Friston KJ, Brown RG, Frackowiak RS, Dolan RJ. Regional cerebral blood flow in depression measured by positron emission tomography: the relationship with clinical dimensions. *Psychol Med* (1993) **23**(3):579–90. doi:10.1017/S0033291700025368
21. Dolan RJ, Bench CJ, Liddle PF, Friston KJ, Frith CD, Grasby PM, et al. Dorsolateral prefrontal cortex dysfunction in the major psychoses; symptom or disease specificity? *J Neurol Neurosurg Psychiatry* (1993) **56**(12):1290–4. doi:10.1136/jnnp.56.12.1290
22. Brody AL, Saxena S, Mandelkern MA, Fairbanks LA, Ho ML, Baxter LR. Brain metabolic changes associated with symptom factor improvement in major depressive disorder. *Biol Psychiatry* (2001) **50**(3):171–8. doi:10.1016/S0006-3223(01)01117-9
23. Mayberg HS, Lewis PJ, Regenold W, Wagner HN Jr. Paralimbic hypoperfusion in unipolar depression. *J Nucl Med* (1994) **35**(6):929–34.
24. Meyer JH, McNeely HE, Sagrati S, Boovariwala A, Martin K, Verhoeff NP, et al. Elevated putamen D(2) receptor binding potential in major depression with motor retardation: an [11C]raclopride positron emission tomography study. *Am J Psychiatry* (2006) **163**(9):1594–602. doi:10.1176/appi.ajp.163.9.1594
25. Frey SH, Fogassi L, Grafton S, Picard N, Rothwell JC, Schweighofer N, et al. Neurological principles and rehabilitation of action disorders: computation, anatomy, and physiology (CAP) model. *Neurorehabil Neural Repair* (2011) **25**(5 Suppl):6S–20S. doi:10.1177/1545968311410940
26. Rizzolatti G, Luppino G. The cortical motor system. *Neuron* (2001) **31**(6):889–901. doi:10.1016/S0896-6273(01)00423-8
27. Mayberg HS, Liotti M, Brannan SK, McGinnis S, Mahurin RK, Jerabek PA, et al. Reciprocal limbic-cortical function and negative mood: converging PET findings in depression and normal sadness. *Am J Psychiatry* (1999) **156**(5):675–82.
28. McGrath CL, Kelley ME, Holtzheimer PE, Dunlop BW, Craighead WE, Franco AR, et al. Toward a neuroimaging treatment selection biomarker for major depressive disorder. *JAMA Psychiatry* (2013) **70**(8):821–9. doi:10.1001/jamapsychiatry.2013.143
29. Seminowicz DA, Mayberg HS, McIntosh AR, Goldapple K, Kennedy S, Segal Z, et al. Limbic-frontal circuitry in major depression: a path modeling metanalysis. *Neuroimage* (2004) **22**(1):409–18. doi:10.1016/j.neuroimage.2004.01.015
30. Austin MP, Mitchell P, Hadzi-Pavlovic D, Hickie I, Parker G, Chan J, et al. Effect of apomorphine on motor and cognitive function in melancholic patients: a preliminary report. *Psychiatry Res* (2000) **97**(2–3):207–15. doi:10.1016/S0165-1781(00)00222-5
31. Liston C, Chen AC, Zebley BD, Drysdale AT, Gordon R, Leuchter B, et al. Default mode network mechanisms of transcranial magnetic stimulation in depression. *Biol Psychiatry* (2014) **76**(7):517–26. doi:10.1016/j.biopsych.2014.01.023
32. Ohnishi T, Hayashi T, Okabe S, Nonaka I, Matsuda H, Iida H, et al. Endogenous dopamine release induced by repetitive transcranial magnetic stimulation over the primary motor cortex: an [11C]raclopride positron emission tomography study in anesthetized macaque monkeys. *Biol Psychiatry* (2004) **55**(5):484–9. doi:10.1016/j.biopsych.2003.09.016
33. Ohnishi T, Matsuda H, Imabayashi E, Okabe S, Takano H, Arai N, et al. rCBF changes elicited by rTMS over DLPFC in humans. *Suppl Clin Neurophysiol* (2004) **57**:715–20. doi:10.1016/S1567-424X(09)70412-X
34. Paillere Martinot ML, Martinot JL, Ringuenet D, Galinowski A, Gallarda T, Bellivier F, et al. Baseline brain metabolism in resistant depression and response to transcranial magnetic stimulation. *Neuropsychopharmacology* (2011) **36**(13):2710–9. doi:10.1038/npp.2011.161
35. McCormick LM, Yamada T, Yeh M, Brumm MC, Thatcher RW. Antipsychotic effect of electroconvulsive therapy is related to normalization of subgenual cingulate theta activity in psychotic depression. *J Psychiatr Res* (2009) **43**(5):553–60. doi:10.1016/j.jpsychires.2008.08.004
36. Tengvar C, Johansson B, Sorensen J. Frontal lobe and cingulate cortical metabolic dysfunction in acquired akinetic mutism: a PET study of the interval form of carbon monoxide poisoning. *Brain Inj* (2004) **18**(6):615–25. doi:10.1080/02699050310001622806
37. Paus T. Primate anterior cingulate cortex: where motor control, drive and cognition interface. *Nat Rev Neurosci* (2001) **2**(6):417–24. doi:10.1038/35077500
38. Palomero-Gallagher N, Vogt BA, Schleicher A, Mayberg HS, Zilles K. Receptor architecture of human cingulate cortex: evaluation of the four-region neurobiological model. *Hum Brain Mapp* (2009) **30**(8):2336–55. doi:10.1002/hbm.20667
39. Yu C, Zhou Y, Liu Y, Jiang T, Dong H, Zhang Y, et al. Functional segregation of the human cingulate cortex is confirmed by functional connectivity based neuroanatomical parcellation. *Neuroimage* (2011) **54**(4):2571–81. doi:10.1016/j.neuroimage.2010.11.018
40. Picard N, Strick PL. Motor areas of the medial wall: a review of their location and functional activation. *Cereb Cortex* (1996) **6**(3):342–53. doi:10.1093/cercor/6.3.342
41. Vogt BA, Berger GR, Derbyshire SW. Structural and functional dichotomy of human midcingulate cortex. *Eur J Neurosci* (2003) **18**(11):3134–44. doi:10.1111/j.1460-9568.2003.03034.x
42. Shima K, Tanji J. Role for cingulate motor area cells in voluntary movement selection based on reward. *Science* (1998) **282**(5392):1335–8. doi:10.1126/science.282.5392.1335
43. Morecraft RJ, Van Hoesen GW. Convergence of limbic input to the cingulate motor cortex in the rhesus monkey. *Brain Res Bull* (1998) **45**(2):209–32. doi:10.1016/S0361-9230(97)00344-4
44. Amiez C, Petrides M. Neuroimaging evidence of the anatomo-functional organization of the human cingulate motor areas. *Cereb Cortex* (2014) **24**(3):563–78. doi:10.1093/cercor/bhs329
45. Procyk E, Wilson CR, Stoll FM, Faraut MC, Petrides M, Amiez C. Midcingulate motor map and feedback detection: converging data from humans and monkeys. *Cereb Cortex* (2014). doi:10.1093/cercor/bhu213
46. Picard N, Strick PL. Imaging the premotor areas. *Curr Opin Neurobiol* (2001) **11**(6):663–72. doi:10.1016/S0959-4388(01)00266-5
47. Paus T, Petrides M, Evans AC, Meyer E. Role of the human anterior cingulate cortex in the control of oculomotor, manual, and speech responses: a positron emission tomography study. *J Neurophysiol* (1993) **70**(2):453–69.
48. Habas C. Functional connectivity of the human rostral and caudal cingulate motor areas in the brain resting state at 3T. *Neuroradiology* (2010) **52**(1):47–59. doi:10.1007/s00234-009-0572-1
49. Takada M, Tokuno H, Hamada I, Inase M, Ito Y, Imanishi M, et al. Organization of inputs from cingulate motor areas to basal ganglia in macaque monkey. *Eur J Neurosci* (2001) **14**(10):1633–50. doi:10.1046/j.0953-816x.2001.01789.x
50. Vogt BA, Fountolakis KN, Samaras D, Kövari E, Vogt LJ, Hof PR. Cingulate neuropathological substrates of depression. In: Vogt BA, editor. *Cingulate Neurobiology and Disease.* Oxford: Oxford University Press (2009). p. xxxiv, 829.
51. First MB, Spitzer RL, Gibbon M, Williams JB. *Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Research Version, Patient Edition (SCID-I/P)*. 4th ed. New York: Biometrics Research Department, New York State Psychiatric Institute (2001).
52. Oldfield RC. The assessment and analysis of handedness: the Edinburgh inventory. *Neuropsychologia* (1971) **9**(1):97–113. doi:10.1016/0028-3932(71)90067-4
53. Asberg M, Montgomery SA, Perris C, Schalling D, Sedvall G. A comprehensive psychopathological rating scale. *Acta Psychiatr Scand Suppl* (1978) (271):5–27. doi:10.1111/j.1600-0447.1978.tb02357.x
54. Hickie I, Mason C, Parker G. Comparative validity of two measures of psychomotor function in patients with severe depression. *J Affect Disord* (1996) **37**(2–3):143–9. doi:10.1016/0165-0327(95)00087-9
55. Turkeltaub PE, Eden GF, Jones KM, Zeffiro TA. Meta-analysis of the functional neuroanatomy of single-word reading: method and validation. *Neuroimage* (2002) **16**(3 Pt 1):765–80. doi:10.1006/nimg.2002.1131
56. Tziortzi AC, Haber SN, Searle GE, Tsoumpas C, Long CJ, Shotbolt P, et al. Connectivity-based functional analysis of dopamine release in the striatum using diffusion-weighted MRI and positron emission tomography. *Cereb Cortex* (2014) **24**(5):1165–77. doi:10.1093/cercor/bhs397
57. Jenkinson M, Bannister P, Brady M, Smith S. Improved optimization for the robust and accurate linear registration and motion correction of brain images. *Neuroimage* (2002) **17**(2):825–41. doi:10.1006/nimg.2002.1132

58. Griffanti L, Salimi-Khorshidi G, Beckmann CF, Auerbach EJ, Douaud G, Sexton CE, et al. ICA-based artefact removal and accelerated fMRI acquisition for improved resting state network imaging. *Neuroimage* (2014) **95**:232–47. doi:10.1016/j.neuroimage.2014.03.034
59. Salimi-Khorshidi G, Douaud G, Beckmann CF, Glasser MF, Griffanti L, Smith SM. Automatic denoising of functional MRI data: combining independent component analysis and hierarchical fusion of classifiers. *Neuroimage* (2014) **90**:449–68. doi:10.1016/j.neuroimage.2013.11.046
60. Smith SM. Fast robust automated brain extraction. *Hum Brain Mapp* (2002) **17**(3):143–55. doi:10.1002/hbm.10062
61. Jenkinson M, Smith S. A global optimisation method for robust affine registration of brain images. *Med Image Anal* (2001) **5**(2):143–56. doi:10.1016/S1361-8415(01)00036-6
62. Woolrich MW, Ripley BD, Brady M, Smith SM. Temporal autocorrelation in univariate linear modeling of FMRI data. *Neuroimage* (2001) **14**(6):1370–86. doi:10.1006/nimg.2001.0931
63. Oakes TR, Fox AS, Johnstone T, Chung MK, Kalin N, Davidson RJ. Integrating VBM into the general linear model with voxelwise anatomical covariates. *Neuroimage* (2007) **34**(2):500–8. doi:10.1016/j.neuroimage.2006.10.007
64. Woolrich MW, Behrens TE, Beckmann CF, Jenkinson M, Smith SM. Multilevel linear modelling for FMRI group analysis using Bayesian inference. *Neuroimage* (2004) **21**(4):1732–47. doi:10.1016/j.neuroimage.2003.12.023
65. Woolrich MW, Jbabdi S, Patenaude B, Chappell M, Makni S, Behrens T, et al. Bayesian analysis of neuroimaging data in FSL. *Neuroimage* (2009) **45**(1 Suppl):S173–86. doi:10.1016/j.neuroimage.2008.10.055
66. Beckmann CF, Jenkinson M, Smith SM. General multilevel linear modeling for group analysis in FMRI. *Neuroimage* (2003) **20**(2):1052–63. doi:10.1016/S1053-8119(03)00435-X
67. Friston KJ, Buechel C, Fink GR, Morris J, Rolls E, Dolan RJ. Psychophysiological and modulatory interactions in neuroimaging. *Neuroimage* (1997) **6**(3):218–29. doi:10.1006/nimg.1997.0291
68. Woo CW, Krishnan A, Wager TD. Cluster-extent based thresholding in fMRI analyses: pitfalls and recommendations. *Neuroimage* (2014) **91**:412–9. doi:10.1016/j.neuroimage.2013.12.058
69. Nudo RJ. Recovery after brain injury: mechanisms and principles. *Front Hum Neurosci* (2013) **7**:887. doi:10.3389/fnhum.2013.00887
70. Wessa M, Houenou J, Paillere-Martinot ML, Berthoz S, Artiges E, Leboyer M, et al. Fronto-striatal overactivation in euthymic bipolar patients during an emotional go/nogo task. *Am J Psychiatry* (2007) **164**(4):638–46. doi:10.1176/appi.ajp.164.4.638
71. Agid Y, Buzsaki G, Diamond DM, Frackowiak R, Giedd J, Girault JA, et al. How can drug discovery for psychiatric disorders be improved? *Nat Rev Drug Discov* (2007) **6**(3):189–201. doi:10.1038/nrd2217
72. Schloesser RJ, Martinowich K, Manji HK. Mood-stabilizing drugs: mechanisms of action. *Trends Neurosci* (2012) **35**(1):36–46. doi:10.1016/j.tins.2011.11.009
73. Logothetis NK, Pfeuffer J. On the nature of the BOLD fMRI contrast mechanism. *Magn Reson Imaging* (2004) **22**(10):1517–31. doi:10.1016/j.mri.2004.10.018
74. Hu Y, Chen X, Gu H, Yang Y. Resting-state glutamate and GABA concentrations predict task-induced deactivation in the default mode network. *J Neurosci* (2013) **33**(47):18566–73. doi:10.1523/JNEUROSCI.1973-13.2013
75. Enzi B, Duncan NW, Kaufmann J, Tempelmann C, Wiebking C, Northoff G. Glutamate modulates resting state activity in the perigenual anterior cingulate cortex – a combined fMRI-MRS study. *Neuroscience* (2012) **227**:102–9. doi:10.1016/j.neuroscience.2012.09.039
76. Greicius MD, Flores BH, Menon V, Glover GH, Solvason HB, Kenna H, et al. Resting-state functional connectivity in major depression: abnormally increased contributions from subgenual cingulate cortex and thalamus. *Biol Psychiatry* (2007) **62**(5):429–37. doi:10.1016/j.biopsych.2006.09.020
77. Grimm S, Boesiger P, Beck J, Schuepbach D, Bermpohl F, Walter M, et al. Altered negative BOLD responses in the default-mode network during emotion processing in depressed subjects. *Neuropsychopharmacology* (2009) **34**(4):932–43. doi:10.1038/npp.2008.81
78. Kuhn S, Gallinat J. Resting-state brain activity in schizophrenia and major depression: a quantitative meta-analysis. *Schizophr Bull* (2013) **39**(2):358–65. doi:10.1093/schbul/sbr151
79. Horn DI, Yu C, Steiner J, Buchmann J, Kaufmann J, Osoba A, et al. Glutamatergic and resting-state functional connectivity correlates of severity in major depression – the role of pregenual anterior cingulate cortex and anterior insula. *Front Syst Neurosci* (2010) **4**:33. doi:10.3389/fnsys.2010.00033
80. Phillips ML, Swartz HA. A critical appraisal of neuroimaging studies of bipolar disorder: toward a new conceptualization of underlying neural circuitry and a road map for future research. *Am J Psychiatry* (2014) **171**(8):829–43. doi:10.1176/appi.ajp.2014.13081008
81. Poldrack RA. Region of interest analysis for fMRI. *Soc Cogn Affect Neurosci* (2007) **2**(1):67–70. doi:10.1093/scan/nsm006
82. Logothetis NK, Pauls J, Augath M, Trinath T, Oeltermann A. Neurophysiological investigation of the basis of the fMRI signal. *Nature* (2001) **412**(6843):150–7. doi:10.1038/35084005
83. Allman JM, Hakeem A, Erwin JM, Nimchinsky E, Hof P. The anterior cingulate cortex. The evolution of an interface between emotion and cognition. *Ann N Y Acad Sci* (2001) **935**:107–17. doi:10.1111/j.1749-6632.2001.tb03476.x
84. Shimoyama I, Ninchoji T, Uemura K. The finger-tapping test. A quantitative analysis. *Arch Neurol* (1990) **47**(6):681–4. doi:10.1001/archneur.1990.00530060095025

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Received: 08 October 2014; accepted: 21 November 2014; published online: 04 December 2014.

*Citation: Liberg B, Klauser P, Harding IH, Adler M, Rahm C, Lundberg J, Masterman T, Wachtler C, Jonsson T, Kristoffersen-Wiberg M, Pantelis C and Wahlund B (2014) Functional and structural alterations in the cingulate motor area relate to decreased fronto-striatal coupling in major depressive disorder with psychomotor disturbances. Front. Psychiatry **5**:176. doi: 10.3389/fpsyt.2014.00176*

This article was submitted to Schizophrenia, a section of the journal Frontiers in Psychiatry.

frontiers in Psychiatry

MINI REVIEW
published: 10 March 2015
doi: 10.3389/fpsyt.2015.00034

The functional anatomy of psychomotor disturbances in major depressive disorder

Benny Liberg [1,2] and Christoffer Rahm [1,3]*

[1] Department of Psychiatry, Melbourne Neuropsychiatry Centre, The University of Melbourne, Melbourne, VIC, Australia, [2] Division of Medical Imaging and Technology, Department of Clinical Science, Intervention and Technology (CLINTEC), Karolinska Institutet, Stockholm, Sweden, [3] Unit of Metabolism, Department of Medicine Huddinge, Karolinska Institutet, Stockholm, Sweden

Psychomotor disturbances (PMD) are a classic feature of depressive disorder that provides rich clinical information. The aim our narrative review was to characterize the functional anatomy of PMD by summarizing findings from neuroimaging studies. We found evidence across several neuroimaging modalities that suggest involvement of fronto-striatal neurocircuitry, and monoaminergic pathways and metabolism. We suggest that PMD in major depressive disorder emerge from an alteration of limbic signals, which influence emotion, volition, higher-order cognitive functions, and movement.

Keywords: psychomotor performance, major depressive disorder, neuroimaging, frontal lobe, basal ganglia, monoamines

OPEN ACCESS

Edited by:
Sebastian Walther, University Hospital of Psychiatry, Switzerland

Reviewed by:
Bernhard J. Mitterauer, Volitronics-Institute for Basic Research Psychopathology and Brain Philosophy, Austria
Jessica A. Turner, Georgia State University, USA
Sebastian Walther, University Hospital of Psychiatry, Switzerland

****Correspondence:***
Benny Liberg, Department of Psychiatry, Melbourne Neuropsychiatry Centre, Alan Gilbert Building, Level 3, 161 Barry Street, Carlton South, Melbourne, VIC 3053, Australia
benny.liberg@gmail.com

Specialty section:
This article was submitted to Schizophrenia, a section of the journal Frontiers in Psychiatry

Received: *19 December 2014*
Accepted: *19 February 2015*
Published: *10 March 2015*

Citation:
Liberg B and Rahm C (2015) The functional anatomy of psychomotor disturbances in major depressive disorder. Front. Psychiatry ***6****:34. doi: 10.3389/fpsyt.2015.00034*

Introduction

Psychomotor signs are a classic feature of major depressive disorder that already attracted attention over a century ago (1). Emil Kraepelin gave a vivid and still valid description of psychomotor disturbances (PMD) in his chapter on general symptomatology in *Lehrbuch des Psychiatrie*, 1907: "The psychomotor retardation, which is the most important disturbance in the depressed states of manic-depressive insanity, is probably due to a [. . .] increase in resistance [. . .] In spite of every apparent exertion, the patients cannot utter a word or at best answer only in monosyllables, and are unable to eat, stand up, or dress. As a rule they clearly recognize the enormous pressure lying upon them, which they are unable to overcome" (2).

Psychomotor disturbances in depressive disorder can be broadly classified in to four subgroups of symptoms and signs based on three available clinical rating scales designed to characterize them [CORE, motor agitation and retardation scale (MARS), Widlöcher scale] (3–5): retardation, agitation, non-interactiveness, and mental slowing (**Table 1**). The symptoms and signs of PMD therefore entail a wide range of brain functions including motor performance, executive function, volition, and drive. These provide rich clinical information (i.e., diagnostic subgroup, prognosis, treatment) (6, 7).

No previous review has focused specifically on neuroimaging findings related to PMD in major depressive disorder. The aim of this narrative review is to characterize the functional anatomy of PMD in major depressive disorder by summarizing findings from human neuroimaging studies that probe structure, function, neurochemistry, and connectivity.

Structural Neuroimaging

Structural aberrations in white matter are the most prominent structural neuroimaging findings associated with PMD in depressive disorder.

TABLE 1 | Psychomotor signs in major depressive disorder.

Subgroup of psychomotor disturbances	Example
Retardation	Slowed movements (motor slowness), facial immobility (lack of facial expressivity, downcast gaze, reduced voice volume, slurring of speech), body immobility (immobility of trunk/proximal limbs), postural slumping (postural collapse), delay in motor activity, delay in responding verbally (delayed speech onset), slowing of speech rate (monotone speech), abnormal gait
Agitation	Frightened apprehension (static facial expression, abnormal staring, increased blinking, erratic eye movement), facial agitation (movement/tension in mouth), motor agitation (increased axial truncal movement), stereotyped movements (tension in fingers and hands, hand movement, foot/lower leg movement), verbal stereotypy
Non-interactiveness	Response to social cues, emotional responsiveness, inattentiveness, poverty of associations, spontaneous speech, length of verbal responses
Mental slowing	Language and verbal flow, variety of themes spontaneously approached, richness of associations, subjective experience of ruminations, fatigability, perception of flow of time, memory, concentration, interest in habitual activities

White-matter alterations (hyperintensities, WHI; and white-matter fiber integrity), are one of the most reproduced findings in mood disorders. White-matter hyperintensities (WHIs) are radiological hyperintense regions of white matter with elusive etiology in MRI images. They are primarily associated with late-life depression, but are also more common in major depressive disorder in younger age groups. The extent of WHIs correlates with illness severity, poor treatment response, and decreased psychomotor speed on several neuropsychological tests (8). White-matter tissue broadly comprises glial cells with myelin surrounding axons. Currently, the general understanding is that the WHIs alterations observed in depression arise from small vessel disease that lead to disruption of white-matter pathways (9). However, other disease mechanisms involving white-matter tissue may also lead to disruptions of specific neurocircuits and lead to psychiatric symptoms such as PMD (10).

White-matter fiber integrity can be assessed with diffusion-weighted imaging. One study by Walther et al. (11) who specifically addressed psychomotor functioning in depressive disorder used diffusion-weighted magnetic resonance imaging and actigraphy – an objective measure of the general activity level in an individual. It showed that lower activity levels correlate with measures of differential myelinization in the frontal lobe and posterior cingulate region, and that there is a negative correlation between the same measures in the white matter beneath the primary motor cortex and in the parahippocampal region. The authors conclude that changes in psychomotor function in depressive disorder may be linked to changes in white matter in motor regions. Bracht et al. used diffusion-weighted imaging to investigate white-matter microstructure in relation to PMD. They found a positive association between decreased physical motor activity and alterations in paralimbic and motor midline regions not only involved in volitional movement but also involvement of ascending mesocortical dopamine pathways in clinical states with prominent PMD (12, 13).

To this date, few studies have investigated the relation between gray matter volume and PMD in major depressive disorder. Current findings involve volume reductions in several pre-executive parts of the motor system. One volumetric study showed that thinning of the right presupplementary motor cortex (pre-SMA) is associated with impaired performance on a motor learning test (14). The pre-SMA is a part of the mesial premotor cortex that advances signals from the prefrontal regions, engaged in higher-order cognitive functions. In studies measuring subcortical volumes and regional shape alterations, no significant associations could be found between performance on a psychomotor task (trail making test variations) and the volumes of striatum, pallidum, and thalamus in depressed subjects (15, 16). Another study found that reduced caudate nucleus volumes predicts decreased psychomotor speed in depressed subjects >50 years old (17).

Only one study, using CT, has assessed cerebrospinal fluid space size. This study found that the size of the third ventricle was associated with clinical ratings of psychomotor retardation (18).

Functional Neuroimaging

Blood–oxygen-level-dependent (BOLD) functional magnetic resonance imaging (fMRI) is currently the most prevalent method for studying neural activation patterns during experimental tasks in patients with depressive disorder. A few research teams have specifically addressed PMD using fMRI and experimental motor tasks, clinical ratings of psychomotor disturbance, or motor physiology metrics (i.e., actigraphy, reaction time). Two types of studies have been employed – *task* and *non-task* based studies. Naismith et al. (19) used a motor sequence task (button press response) to study motor learning, and found increased activation of lateral prefrontal cortex, superior temporal regions, and the cerebellum. Caligiuri et al. (20, 21) studied motor execution using a manual reaction time task, and found increased activation during movement in the primary motor cortex, alongside motor asymmetry. Five other studies investigated motor speed using different finger-tapping variations (22–27), and suggest an increased activation in both motor and paralimbic regions, and with altered fronto-striatal coupling among patients. One non-task, resting-state study, by Yao et al. (28) corroborates the hyperactivation of paralimbic regions in patients.

Electroencephalography

Electroencephalography (EEG) is used to study power amplitude of particular frequency spectrums, hemisphere asymmetry, and chronometric features of cortical neural activation. PMD have been associated with greater variability and increased amplitudes in the delta (<4 Hz) and theta (4–7 Hz) spectrum, but not with hemisphere asymmetry (29). The post-imperative negative variation is a metric related to frontal lobe function, and has been associated with psychomotor slowing in a choice reaction task

(30). Another frontal metric (P300) has also been correlated positively correlated with PMD (31). Interestingly, this study also showed that only clinical ratings more focused on PMD than the Hamilton depression ratings scale (HDRS) predicted P300 latency. In a group of patients receiving electroconvulsive treatment, clinical ratings of PMD were positively correlated with frequency decreases during initial improvement, whereas the reverse relationship was found during the later partial remission phase (32). One study by Nieber et al. (33) showed a positive correlation between decreased frequencies in particular regions of the theta and alpha (7–13 Hz) spectrum and overall retardation, with motor retardation, in particular. In that study, increased frequency in particular regions of in the alpha and beta spectrum was negatively correlated with PMD. Error-related negativity and positive-negativity are metrics associated with anterior and posterior cingulate cortex function, respectively (34, 35). These metrics have been associated with a slowing of psychomotor performance in subjects during action monitoring, but only positive-negativity differentiated patients and controls (36).

Molecular Neuroimaging

Single-photon emission tomography (SPECT), positron emission tomography (PET), and arterial spin labeling (ASL) are the three molecular neuroimaging methods that have been used to study PMD. These three methods measure regional cerebral blood flow, glucose metabolism, oxygen consumption, or synaptic transmission factors. Walther et al. (37) used ASL and actigraphy to measure the correlation between regional cerebral blood flow and general motor activity outside of the scanner environment in depressed subjects. The study showed a positive correlation between physical activity and blood perfusion in the right orbitofrontal cortex, and a negative correlation with left supplementary motor area perfusion. The available evidence from PET and SPECT studies also suggests that PMD in depression are associated with decreased DLPFC metabolism (38–40), increased ACC metabolism (41–43), and a lower dopaminergic tone and altered metabolism in striatal regions (41, 42, 44–47). However, a SPECT study by Graff-Guerrero et al. (48) failed to reproduce these associations between clinical rating of PMD and cerebral blood flow. One longitudinal study also suggests that improvement of psychomotor slowing is associated with increased activation in the dorsal ACC (49).

Transcranial Ultrasound

Hypo- or hyperechogenicity measured by transcranial sonography *in vivo* reflect changes in tissue impedance, likely due to alterations of microarchitecture such as shifts in cell density, changes in interstitial matrix composition, or alterations of fiber tract integrity (50, 51). Those transcranial ultrasound studies that have investigated PMD in major depression have focused on the serotonergic raphe nuclei and the dopaminergic substantia nigrae. A significantly reduced echogenicity of the mesencephalic midline raphe nuclei has been reported in depressed subjects (52). Hypoechogenicity of the raphe nuclei can be found in 50–70% of unipolar depressed subjects compared to 10% in healthy subjects (53). Hypoechogenicity of the raphe nuclei of the brain stem is associated with better treatment response to serotonin reuptake inhibitors (54) and with symptom severity in suicidal ideation (55). One study could not find any association between echogenicity of the raphe nuclei and PMD (51), another found a positive correlation with the degree of psychomotor retardation (56), and a third a negative correlation with psychomotor retardation (54). Hoeppner et al. showed that substantia nigra echogenic size correlates with motor asymmetry and reduced verbal fluency in unipolar depression. In that study, the association was stronger in patients $\geq$50 years, and in patients with reduced brain stem raphe nuclei hypogenicity (57).

Conclusion

In this review, we summarize the literature on the functional neuroanatomy of PMD in major depressive disorder (**Table 2**). Despite the clinical importance of PMD, we found relatively few studies. Indeed, the motor system has been relatively neglected in brain imaging studies of psychiatric disorders in general (58). We conclude that structural alterations that correlate with PMD have been found in gray- and white-matter regions within several nodes of cortico-subcortical circuits. Findings in functional neuroimaging studies show involvement of the same neurocircuitry nodes (along with their white-matter connections) as in structural neuroimaging studies, and further that limbic influences on the motor system may be important in the emergence of PMD. EEG studies suggest that frequency variations across many spectra, and an involvement of the frontal cortex, anterior, and posterior cingulate cortex, are associated with PMD. The molecular neuroimaging correlates of PMD resemble the functional anatomy of major depression described with functional and structural methods, but in addition also implicate disrupted monoamine transmission in PMD. The few available studies that use transcranial ultrasound primarily show an association between PMD and echogenic features of the substantia nigra, which then corroborates molecular neuroimaging findings of disrupted dopamine transmission.

Structural and functional neuroimaging studies suggest that PMD involve alterations in large-scale cortico-striato-thalamo-cortical neurocircuits, and in particular fronto-striatal subdivisions. Findings from transcranial ultrasound, and molecular neuroimaging studies, suggest a putative underlying factor for these alterations in the form of disrupted influence of ascending dopamine tracts that emanate from deeper midbrain nuclei. This notion also fits with the broader picture of a depressive disorder with psychomotor disturbances, which also include alterations in cognitive function, drive, and emotional expression – phenomena that also map onto ascending monoamine tracts with targets in the frontal lobe. Taken together, the broad picture suggests that PMD in major depressive disorder emerges from altered limbic signals at the interface of emotion, volition, higher-order cognitive function, and movement.

Our review shows that PMD is an emerging field of research that has kept growing since over 20 years. However, the currently available studies also preclude firmer evidence when evaluated

TABLE 2 | Neuroimaging findings and their correlation to psychomotor disturbances.

	Study	*N*	Diagnosis	Method	Measure	Finding
Structural CT and MRI	Hickie et al. (8)	39	MDD	MRI (WMH)	Mean decision time	↑ White-matter hyperintensities
	Walther et al. (11)	21	MDD	DTI (FA)	Actigraphy	↓ White-matter in motor regions
	Bracht et al. (12)	21/21	MDD	DTI (FA)	Actigraphy	↓ White-matter in ACC and midline motor regions connected with PFC
	Bracht et al. (13)	22/21	MDD	DTI (FA)	Clinical features of PMD	↓ White-matter in medial forebrain bundle
	Exner et al. (14)	9	MDD	MRI (ROI)	Serial reaction time task	↓ pre-SMA volume
	Liberg et al. (15)	27	BPD	MRI (ROI, shape)	Trail Making Tests, reaction Time	No significant findings in the striatum, pallidum, and the thalamus
	Liberg et al. (16)	20	BPD	MRI (ROI, shape)	Trail Making Tests	No significant findings in the striatum, pallidum, and the thalamus
	Naismith et al. (17)	47	MDD	MRI (ROI)	Trail Making Test A	↓ Right caudate volume
	Schlegel et al. (18)	44	MDD	CT, ventricle size	Bech–Rafaelsen Melancholia Scale	↑ Lateral ventricle size
fMRI	Naismith et al. (19)	19/20	MDD	Task-based fMRI	Motor sequencing task	↑ Middle frontal gyrus, superior temporal gyrus, and cerebellum
	Caligiuri et al. (20)	24/13	BPD	Task-based fMRI	Manual reaction time task	↑ Right primary motor cortex in patients
	Caligiuri et al. (21)	18/13	BPD	Task-based fMRI	Manual reaction time task	↑ Left primary motor area in patients. Motor asymmetry in patients with a failure to suppress right hemisphere activation during movement
	Marchand et al. (22)	10	BPD	Task-based fMRI	Finger-tapping	↑ Right anterior cingulate cortex and medial frontal gyrus (euthymia > depression)
	Liberg et al. (24)	9/12	BPD	Task-based fMRI	Finger-tapping	No significant findings
	Liberg et al. (25)	9/12	BPD	Task-based fMRI	Finger-tapping, Motor imagery, CORE, AS-18	↓ Primary motor cortex, lateral ventral premotor cortex in relation to clinical ratings. ↑ Medial posterior parietal cortex during motor imagery. ↑ Fronto-parietal regions, and insular cortex, during motor execution
	Liberg et al. (26)	13/13	MDD	Task-based fMRI	Finger-tapping	↓ Fronto-striatal coupling between cingulate motor area and putamen. ↑ Left cingulate motor area. ↑ Functional coupling and clinical ratings
	Marchand et al. (27)	14/15	BPD	Task-based fMRI	Finger-tapping	↑ Left pre- and post-central gyrus, bilateral cingulate, right striatum, and left striatum, in patients
	Yao et al. (28)	22/22	MDD	Resting-state fMRI	HDRS	↑ Regional homogeneity in right posterior cingulate cortex and right insula
EEG	Nyström et al. (29)	25	MDD	EEG power spectrum analysis	Comprehensive Psychopatho-logical Rating Scale	↑ Delta-, theta-amplitude, and variability
	Thier et al. (30)	11/11	MDD	ERP	Serial choice reaction task	↑ Post-imperative negative variation
	Schlegel et al. (31)	36	MDD	ERP	Bech–Rafaelsen Melancholia Scale	↑ P300 latency
	Silfverskiöld et al. (32)	21	MDD	Global EEG frequency	Rating Scale for Affective Symptoms	↓ Acute effects ↑ Non-acute effects
	Nieber et al. (33)	63	MDD	EEG power spectrum analysis	Bech–Rafaelsen Melancholia Scale	↑ Slow activity ↓ Fast activity
	Schrijvers et al. (36)	26	MDD	ERP, Eriksen Flanker's Task	Salpêtrière Retardation Rating Scale	↑ Error-related negativity potentials

(Continued)

TABLE 2 | Continued

	Study	*N*	Diagnosis	Method	Measure	Finding
Molecular neuroimaging	Walther et al. (37)	20/19	MDD	ASL	Wrist actigraphy	↑ Right orbitofrontal cortex, ↓ left SMA
	Bench et al. (38)	40	MDD	PET	HDRS	↓ rCBF in left DLPFC, left parietal cortex
	Dolan et al. (39)	40	MDD	PET	HDRS	↓ rCBF in left DLPFC
	Videbech et al. (40)	42	MDD	PET	HDRS	↓ rCBF in DLPFC and OFC
	Milak et al. (41)	298	MDD	FDG-PET	HDRS	↑ Metabolism in the cingulate gyrus, thalamus, and basal ganglia
	Dunn et al. (42)	58	MDD	FDG-PET	Beck's Depression Inventory	↓ Metabolism in right insula, claustrum, anteroventral caudate/putamen, and temporal cortex.
						↑ Metabolism in ACC
	Mayberg et al. (43)	13	MDD	99mTc-SPECT	Finger-tapping	↑ rCBF in paralimbic cortex (frontal and temporal) and prefrontal
	Meyer et al. (44)	9/21	MDD	RTI-32-PET	Finger-tapping	↓ Dopamine transporter binding potential in striatum
	Meyer et al. (45)	21	MDD	Raclopride PET	Finger-tapping	↑ Dopamine D2 receptor binding potential in the putamen
	Ebert et al. (46)	20	MDD	IBZM-SPECT	–	↑ Striatal IBZM-BP
	Perico et al. (47)	15	MDD	99mTc-SPECT	HDRS	↑ Left premotor cortex and right anterior medial orbitofrontal cortex metabolism
	Graff-Guerrero et al. (48)	14	MDD	99mTc-SPECT	HDRS	No significant correlation between retardation and CBF
	Brody et al. (49)	39	MDD	FDG-PET	HDRS	Improvement in psychomotor symptoms is associated with metabolism in dorsal ACC
Transcranial sonography	Berg et al. (51)	31	PD with MDD	Ncl raphe	Columbia University Rating Scale	No significant correlation
	Walter et al. (53)	55	MDD	Ncl raphe, substantia nigra	Unified Parkinson's Disease Rating Scale (Motor part)	↓ Raphe echogenicity, ↑ Substantia nigra echogenecity
	Walter et al. (54)	52	MDD	Ncl raphe	Motor Retardation and Agitation Scale	↑ Raphe echogenecity
	Becker et al. (56)	30	PD with MDD	Ncl raphe	Columbia University Rating Scale	↓ Raphe echogenecity
	Höppner et al. (57)	45	MDD	Substantia nigra	Finger-tapping (motor asymmetry), verbal fluency	↑ Substantia nigra echogenic size

ACC, anterior cingulate cortex; AS-18, affektiv skattningsskala 18 (59); ASL, arterial spin labeling; BP, binding potential; BPD, bipolar disorder depression; CT, computed tomography; DTI, diffusion tensor imaging; DLPFC, dorsolateral prefrontal cortex; EEG, electroencephalography; ERP, event-related potentials; FA, fractional anisotropy; FDG-PET, fluorodeoxyglucose positron emission tomography; fMRI, functional magnetic resonance imaging; HDRS, Hamilton Depression Rating Scale; IBZM, iodobenzamide single-photon emission computed tomography; MDD, major depressive disorder; MRI, magnetic resonance imaging; OFC, orbitofrontal cortex; PD, Parkinson's disease; PET, positron emission tomography; ROI, region of interest; rCBF, regional cerebral blood flow; RTI-32, (1R-2-exo-3-exo)-8-methyl-3-(4-methylphenyl)-8-azabicyclo[3.2.1]octane-2-carboxylate; SMA, supplementary motor area; SPECT, single-photon emission computed tomography; 99mTc, Technetium-99.

in the context of general research methodology. Most studies are cross-sectional, have <25 participants, and have not been reproduced. Furthermore, a wide variety of clinical psychomotor measures have been used. Thus, information about the anatomical specificity of PMD from future studies could be improved by the use of objective measurements of motor performance (i.e., finger-tapping, actigraphy) when investigating the different dimensions of PMD delineated by current clinical measurements (i.e., CORE, MARS), and using rating scales that probe PMD specifically. Further studies would also benefit from longitudinal experimental designs that disentangle the effects of brain changes on the functional components of PMD, and assess differences across neuropsychiatric disorders.

Acknowledgments

BL received funding from Svenska Läkaresällskapet (The Swedish Society of Medicine, SLS-403101), and the Strategic Research Committee, Karolinska Institutet/Stockholm County Council, Sweden. CR received funding from Schizofreniförbundet, Sweden. We also thank Dr. Caroline Wachtler for language revisions of the manuscript.

References

1. Wells FL. Motor retardation as a manic-depressive symptom. *Am J Insanity* (1909) **LXVI**(1):1–51.
2. Kraepelin E, Diefendorf AR. *Clinical Psychiatry*. (Vol. xvii). New York, NY: The Macmillan Company (1907). 562 p.
3. Parker G, Hadzi-Pavlovic D, Brodaty H, Boyce P, Mitchell P, Wilhelm K, et al. Psychomotor disturbance in depression: defining the constructs. *J Affect Disord* (1993) **27**(4):255–65. doi:10.1016/0165-0327(93)90049-P
4. Sobin C, Mayer L, Endicott J. The motor agitation and retardation scale: a scale for the assessment of motor abnormalities in depressed patients. *J Neuropsychiatry Clin Neurosci* (1998) **10**(1):85–92. doi:10.1176/jnp.10.1.85
5. Widlocher DJ. Psychomotor retardation: clinical, theoretical, and psychometric aspects. *Psychiatr Clin North Am* (1983) **6**(1):27–40.
6. Malhi GS, Berk M. Does dopamine dysfunction drive depression? *Acta Psychiatr Scand Suppl* (2007) **433**:116–24. doi:10.1111/j.1600-0447.2007.00969.x
7. Malhi GS, Parker GB, Greenwood J. Structural and functional models of depression: from sub-types to substrates. *Acta Psychiatr Scand* (2005) **111**(2):94–105. doi:10.1111/j.1600-0447.2004.00475.x
8. Hickie I, Scott E, Mitchell P, Wilhelm K, Austin MP, Bennett B. Subcortical hyperintensities on magnetic resonance imaging: clinical correlates and prognostic significance in patients with severe depression. *Biol Psychiatry* (1995) **37**(3):151–60. doi:10.1016/0006-3223(94)00174-2
9. Wang L, Leonards CO, Sterzer P, Ebinger M. White matter lesions and depression: a systematic review and meta-analysis. *J Psychiatr Res* (2014) **56**:56–64. doi:10.1016/j.jpsychires.2014.05.005
10. Najjar S, Pearlman DM. Neuroinflammation and white matter pathology in schizophrenia: systematic review. *Schizophr Res* (2015) **161**(1):102–12. doi:10.1016/j.schres.2014.04.041
11. Walther S, Hugli S, Hofle O, Federspiel A, Horn H, Bracht T, et al. Frontal white matter integrity is related to psychomotor retardation in major depression. *Neurobiol Dis* (2012) **47**(1):13–9. doi:10.1016/j.nbd.2012.03.019
12. Bracht T, Federspiel A, Schnell S, Horn H, Hofle O, Wiest R, et al. Cortico-cortical white matter motor pathway microstructure is related to psychomotor retardation in major depressive disorder. *PLoS One* (2012) **7**(12):e52238. doi:10.1371/journal.pone.0052238
13. Bracht T, Horn H, Strik W, Federspiel A, Schnell S, Hofle O, et al. White matter microstructure alterations of the medial forebrain bundle in melancholic depression. *J Affect Disord* (2014) **155**:186–93. doi:10.1016/j.jad.2013.10.048
14. Exner C, Lange C, Irle E. Impaired implicit learning and reduced pre-supplementary motor cortex size in early-onset major depression with melancholic features. *J Affect Disord* (2009) **119**(1–3):156–62. doi:10.1016/j.jad.2009.03.015
15. Liberg B, Ekman CJ, Sellgren C, Johansson A, Landen M. Vertex-based morphometry in euthymic bipolar disorder implicates striatal regions involved in psychomotor function. *Psychiatry Res* (2014) **221**(3):173–8. doi:10.1016/j.pscychresns.2014.01.007
16. Liberg B, Ekman CJ, Sellgren C, Johansson AG, Landen M. Subcortical morphometry and psychomotor function in euthymic bipolar disorder with a history of psychosis. *Brain Imaging Behav* (2014). doi:10.1007/s11682-014-9313-0
17. Naismith S, Hickie I, Ward PB, Turner K, Scott E, Little C, et al. Caudate nucleus volumes and genetic determinants of homocysteine metabolism in the prediction of psychomotor speed in older persons with depression. *Am J Psychiatry* (2002) **159**(12):2096–8. doi:10.1176/appi.ajp.159.12.2096
18. Schlegel S, Maier W, Philipp M, Aldenhoff JB, Heuser I, Kretzschmar K, et al. Computed tomography in depression: association between ventricular size and psychopathology. *Psychiatry Res* (1989) **29**(2):221–30. doi:10.1016/0165-1781(89)90037-1
19. Naismith SL, Lagopoulos J, Ward PB, Davey CG, Little C, Hickie IB. Fronto-striatal correlates of impaired implicit sequence learning in major depression: an fMRI study. *J Affect Disord* (2010) **125**(1–3):256–61. doi:10.1016/j.jad.2010.02.114
20. Caligiuri MP, Brown GG, Meloy MJ, Eberson SC, Kindermann SS, Frank LR, et al. An fMRI study of affective state and medication on cortical and subcortical brain regions during motor performance in bipolar disorder. *Psychiatry Res* (2003) **123**(3):171–82. doi:10.1016/S0925-4927(03)00075-1
21. Caligiuri MP, Brown GG, Meloy MJ, Eyler LT, Kindermann SS, Eberson S, et al. A functional magnetic resonance imaging study of cortical asymmetry in bipolar disorder. *Bipolar Disord* (2004) **6**(3):183–96. doi:10.1111/j.1399-5618.2004.00116.x
22. Marchand WR, Lee JN, Thatcher J, Thatcher GW, Jensen C, Starr J. A preliminary longitudinal fMRI study of frontal-subcortical circuits in bipolar disorder using a paced motor activation paradigm. *J Affect Disord* (2007) **103**(1–3):237–41. doi:10.1016/j.jad.2007.01.008
23. Marchand WR, Lee JN, Thatcher JW, Thatcher GW, Jensen C, Starr J. A longitudinal functional magnetic resonance imaging study of frontal-subcortical circuits in bipolar disorder using a paced motor activation paradigm. *Bipolar Disord* (2007) **9**:74–5.
24. Liberg B, Adler M, Jonsson T, Landen M, Rahm C, Wahlund LO, et al. The neural correlates of self-paced finger tapping in bipolar depression with motor retardation. *Acta Neuropsychiatr* (2013) **25**(1):43–51. doi:10.1111/j.1601-5215.2012.00659.x
25. Liberg B, Adler M, Jonsson T, Landen M, Rahm C, Wahlund LO, et al. Motor imagery in bipolar depression with slowed movement. *J Nerv Ment Dis* (2013) **201**(10):885–93. doi:10.1097/NMD.0b013e3182a5c2a7
26. Liberg B, Klauser P, Harding IH, Adler M, Rahm C, Lundberg J, et al. Functional and structural alterations in the cingulate motor area relate to decreased fronto-striatal coupling in major depressive disorder with psychomotor disturbances. *Front Psychiatry* (2014) **5**:176. doi:10.3389/fpsyt.2014.00176
27. Marchand WR, Lee JN, Thatcher GW, Jensen C, Stewart D, Dilda V, et al. A functional MRI study of a paced motor activation task to evaluate frontal-subcortical circuit function in bipolar depression. *Psychiatry Res* (2007) **155**(3):221–30. doi:10.1016/j.pscychresns.2007.03.003
28. Yao Z, Wang L, Lu Q, Liu H, Teng G. Regional homogeneity in depression and its relationship with separate depressive symptom clusters: a resting-state fMRI study. *J Affect Disord* (2009) **115**(3):430–8. doi:10.1016/j.jad.2008.10.013
29. Nystrom C, Matousek M, Hallstrom T. Relationships between EEG and clinical characteristics in major depressive disorder. *Acta Psychiatr Scand* (1986) **73**(4):390–4. doi:10.1111/j.1600-0447.1986.tb02700.x
30. Thier P, Axmann D, Giedke H. Slow brain potentials and psychomotor retardation in depression. *Electroencephalogr Clin Neurophysiol* (1986) **63**(6):570–81. doi:10.1016/0013-4694(86)90144-6
31. Schlegel S, Nieber D, Herrmann C, Bakauski E. Latencies of the P300 component of the auditory event-related potential in depression are related to the Bech-Rafaelsen melancholia scale but not to the Hamilton rating scale for depression. *Acta Psychiatr Scand* (1991) **83**(6):438–40. doi:10.1111/j.1600-0447.1991.tb05571.x
32. Silfverskiold P, Rosen I, Risberg J, Gustafson L. Changes in psychiatric symptoms related to EEG and cerebral blood flow following electroconvulsive therapy in depression. *Eur Arch Psychiatry Neurol Sci* (1987) **236**(4):195–201. doi:10.1007/BF00383849
33. Nieber D, Schlegel S. Relationships between psychomotor retardation and EEG power spectrum in major depression. *Neuropsychobiology* (1992) **25**(1):20–3. doi:10.1159/000118804
34. Miltner WH, Lemke U, Weiss T, Holroyd C, Scheffers MK, Coles MG. Implementation of error-processing in the human anterior cingulate cortex: a source analysis of the magnetic equivalent of the error-related negativity. *Biol Psychol* (2003) **64**(1–2):157–66. doi:10.1016/S0301-0511(03)00107-8
35. Vocat R, Pourtois G, Vuilleumier P. Unavoidable errors: a spatio-temporal analysis of time-course and neural sources of evoked potentials associated with error processing in a speeded task. *Neuropsychologia* (2008) **46**(10):2545–55. doi:10.1016/j.neuropsychologia.2008.04.006
36. Schrijvers D, de Bruijn ER, Maas Y, De Grave C, Sabbe BG, Hulstijn W. Action monitoring in major depressive disorder with psychomotor retardation. *Cortex* (2008) **44**(5):569–79. doi:10.1016/j.cortex.2007.08.014
37. Walther S, Hofle O, Federspiel A, Horn H, Hugli S, Wiest R, et al. Neural correlates of disbalanced motor control in major depression. *J Affect Disord* (2012) **136**(1–2):124–33. doi:10.1016/j.jad.2011.08.020
38. Bench CJ, Friston KJ, Brown RG, Frackowiak RS, Dolan RJ. Regional cerebral blood flow in depression measured by positron emission tomography: the relationship with clinical dimensions. *Psychol Med* (1993) **23**(3):579–90. doi:10.1017/S0033291700025368
39. Dolan RJ, Bench CJ, Liddle PF, Friston KJ, Frith CD, Grasby PM, et al. Dorsolateral prefrontal cortex dysfunction in the major psychoses; symptom or disease specificity? *J Neurol Neurosurg Psychiatry* (1993) **56**(12):1290–4. doi:10.1136/jnnp.56.12.1290

40. Videbech P, Ravnkilde B, Pedersen TH, Hartvig H, Egander A, Clemmensen K, et al. The Danish PET/depression project: clinical symptoms and cerebral blood flow. A regions-of-interest analysis. *Acta Psychiatr Scand* (2002) **106**(1):35–44. doi:10.1034/j.1600-0447.2002.02245.x
41. Milak MS, Parsey RV, Keilp J, Oquendo MA, Malone KM, Mann JJ. Neuroanatomic correlates of psychopathologic components of major depressive disorder. *Arch Gen Psychiatry* (2005) **62**(4):397–408. doi:10.1001/archpsyc.62.4.397
42. Dunn RT, Kimbrell TA, Ketter TA, Frye MA, Willis MW, Luckenbaugh DA, et al. Principal components of the Beck depression inventory and regional cerebral metabolism in unipolar and bipolar depression. *Biol Psychiatry* (2002) **51**(5):387–99. doi:10.1016/S0006-3223(01)01244-6
43. Mayberg HS, Lewis PJ, Regenold W, Wagner HN Jr. Paralimbic hypoperfusion in unipolar depression. *J Nucl Med* (1994) **35**(6):929–34.
44. Meyer JH, Kruger S, Wilson AA, Christensen BK, Goulding VS, Schaffer A, et al. Lower dopamine transporter binding potential in striatum during depression. *Neuroreport* (2001) **12**(18):4121–5. doi:10.1097/00001756-200112210-00052
45. Meyer JH, McNeely HE, Sagrati S, Boovariwala A, Martin K, Verhoeff NP, et al. Elevated putamen D(2) receptor binding potential in major depression with motor retardation: an [11C]raclopride positron emission tomography study. *Am J Psychiatry* (2006) **163**(9):1594–602. doi:10.1176/ajp.2006.163.9.1594
46. Ebert D, Feistel H, Loew T, Pirner A. Dopamine and depression – striatal dopamine D2 receptor SPECT before and after antidepressant therapy. *Psychopharmacology* (1996) **126**(1):91–4. doi:10.1007/BF02246416
47. Perico CA, Skaf CR, Yamada A, Duran F, Buchpiguel CA, Castro CC, et al. Relationship between regional cerebral blood flow and separate symptom clusters of major depression: a single photon emission computed tomography study using statistical parametric mapping. *Neurosci Lett* (2005) **384**(3):265–70. doi:10.1016/j.neulet.2005.04.088
48. Graff-Guerrero A, Gonzalez-Olvera J, Mendoza-Espinosa Y, Vaugier V, Garcia-Reyna JC. Correlation between cerebral blood flow and items of the Hamilton rating scale for depression in antidepressant-naive patients. *J Affect Disord* (2004) **80**(1):55–63. doi:10.1016/S0165-0327(03)00049-1
49. Brody AL, Saxena S, Mandelkern MA, Fairbanks LA, Ho ML, Baxter LR. Brain metabolic changes associated with symptom factor improvement in major depressive disorder. *Biol Psychiatry* (2001) **50**(3):171–8. doi:10.1016/S0006-3223(01)01117-9
50. Becker G, Berg D, Lesch KP, Becker T. Basal limbic system alteration in major depression: a hypothesis supported by transcranial sonography and MRI findings. *Int J Neuropsychopharmacol* (2001) **4**(1):21–31. doi:10.1017/S1461145701002164
51. Berg D, Supprian T, Hofmann E, Zeiler B, Jager A, Lange KW, et al. Depression in Parkinson's disease: brainstem midline alteration on transcranial sonography and magnetic resonance imaging. *J Neurol* (1999) **246**(12):1186–93. doi:10.1007/s004150050541
52. Becker G, Struck M, Bogdahn U, Becker T. Echogenicity of the brainstem raphe in patients with major depression. *Psychiatry Res* (1994) **55**(2):75–84. doi:10.1016/0925-4927(94)90002-7
53. Walter U, Hoeppner J, Prudente-Morrissey L, Horowski S, Herpertz SC, Benecke R. Parkinson's disease-like midbrain sonography abnormalities are frequent in depressive disorders. *Brain* (2007) **130**(Pt 7):1799–807. doi:10.1093/brain/awm017
54. Walter U, Prudente-Morrissey L, Herpertz SC, Benecke R, Hoeppner J. Relationship of brainstem raphe echogenicity and clinical findings in depressive states. *Psychiatry Res* (2007) **155**(1):67–73. doi:10.1016/j.pscychresns.2006.12.001
55. Budisic M, Karlovic D, Trkanjec Z, Lovrencic-Huzjan A, Vukovic V, Bosnjak J, et al. Brainstem raphe lesion in patients with major depressive disorder and in patients with suicidal ideation recorded on transcranial sonography. *Eur Arch Psychiatry Clin Neurosci* (2010) **260**(3):203–8. doi:10.1007/s00406-009-0043-z
56. Becker T, Becker G, Seufert J, Hofmann E, Lange KW, Naumann M, et al. Parkinson's disease and depression: evidence for an alteration of the basal limbic system detected by transcranial sonography. *J Neurol Neurosurg Psychiatry* (1997) **63**(5):590–6. doi:10.1136/jnnp.63.5.590
57. Hoeppner J, Prudente-Morrissey L, Herpertz SC, Benecke R, Walter U. Substantia nigra hyperechogenicity in depressive subjects relates to motor asymmetry and impaired word fluency. *Eur Arch Psychiatry Clin Neurosci* (2009) **259**(2):92–7. doi:10.1007/s00406-008-0840-9
58. Kupferschmidt DA, Zakzanis KK. Toward a functional neuroanatomical signature of bipolar disorder: quantitative evidence from the neuroimaging literature. *Psychiatry Res* (2011) **193**(2):71–9. doi:10.1016/j.pscychresns.2011.02.011
59. Adler M, Liberg B, Andersson S, Isacsson G, Hetta J. Development and validation of the affective self rating scale for manic, depressive, and mixed affective states. *Nord J Psychiatry* (2008) **62**(2):130–5. doi:10.1080/08039480801960354

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in PSYCHIATRY

ORIGINAL RESEARCH ARTICLE
published: 06 August 2014
doi: 10.3389/fpsyt.2014.00091

Neurological abnormalities in recent-onset schizophrenia and Asperger-syndrome

Dusan Hirjak[1]*, Robert Christian Wolf[1,2], Sabine C. Koch[3], Laura Mehl[1], Janna K. Kelbel[1], Katharina Maria Kubera[1], Tanja Traeger[4], Thomas Fuchs[1] and Philipp Arthur Thomann[1]

[1] Department of General Psychiatry, Center for Psychosocial Medicine, University of Heidelberg, Heidelberg, Germany
[2] Department of Psychiatry, Psychotherapy and Psychosomatics, Saarland University, Homburg, Germany
[3] Department of Dance Movement Therapy, Faculty of Therapeutic Sciences, SRH University Heidelberg, Heidelberg, Germany
[4] Personality, Psychological Assessment, and Psychological Methods, Department of Psychology, University of Koblenz Landau, Landau, Germany

Edited by:
Sebastian Walther, University Hospital of Psychiatry of Bern, Switzerland

Reviewed by:
Einar Patrick Wilder-Smith, National University of Singapore, Singapore
Tobias Bracht, Cardiff University Brain Research Imaging Centre, UK
Lise Docx, University of Antwerp, Belgium

***Correspondence:**
Dusan Hirjak, Department of General Psychiatry, Center for Psychosocial Medicine, University of Heidelberg, Voßstraße 4, D-69115 Heidelberg, Germany
e-mail: dusan.hirjak@med.uni-heidelberg.de

Background: Neurological abnormalities including a variety of subtle deficits such as discrete impairments in sensory integration, motor coordination (MOCO), and sequencing of complex motor acts are frequently found in patients with schizophrenia (SZ) and commonly referred to as neurological soft signs (NSS). Asperger-syndrome (AS) is characterized by sensory-motor difficulties as well. However, the question whether the two disorders share a common or a disease-specific pattern of NSS remains unresolved.

Method: A total of 78 age- and education-matched participants [26 patients with recent-onset SZ, 26 individuals with AS, and 26 healthy controls (HC)] were recruited for the study. Analyses of covariance (ANCOVAs), with age, years of education, and medication included as covariates, were used to examine group differences on total NSS and the five subscale scores. Discriminant analyses were employed to identify the NSS subscales that maximally discriminate between the three groups.

Results: Significant differences among the three groups were found in NSS total score and on the five NSS subscales. The clinical groups differed significantly in the NSS subscale MOCO. The correct discriminant rate between patients with SZ and individuals with AS was 61.5%. The correct discriminant rate was 92.3% between individuals with AS and HC, and 80.8% between SZ patients and HC, respectively.

Conclusion: Our findings provide new evidence for the presence of NSS in AS and lend further support to previously reported difficulties in movement control in this disorder. According to the present results, SZ and AS seem to be characterized by both quantitative and qualitative NSS expression.

Keywords: NSS, motor abnormalities, recent-onset schizophrenia, Asperger-syndrome

INTRODUCTION

Neurological soft signs (NSS) are neurological abnormalities including a variety of subtle deficits such as discrete impairments in sensory integration, motor coordination, sequencing of complex motor acts, clumsiness, and occurrence of primitive reflexes (1–3). A higher prevalence of NSS has been consistently demonstrated not only in patients with clinically manifest schizophrenia (SZ) but also in their non-psychotic first-degree relatives (4). Recent studies indicated that NSS are not only restricted to SZ but are also present in bipolar disorders, depression, obsessive–compulsive disorders (OCD), and other forms of psychosis (5). Nevertheless, previous studies have assessed the power of NSS to discriminate between SZ and other neuropsychiatric disorders. In particular, SZ patients have significantly higher NSS levels than individuals with OCD (6, 7), alcohol dependence (8), bipolar disorders (9, 10), depression (11), and mixed psychiatric diagnoses (12). From a neurobiological point of view, the prefix "soft" indicates that NSS refer to a non-specific or global cerebral dysfunction rather than to impairments of specific or distinct brain regions. Recent magnetic resonance imaging (MRI) studies on SZ found that increased NSS levels are related to aberrant brain morphology within cortical (13–15) and subcortical regions (13, 16–20). Furthermore, the aforementioned studies converge on the conclusion that NSS should be discussed as potential endophenotypes for SZ (4).

In 1911, a renowned German psychiatrist named Eugen Bleuler introduced the concept of accessory and fundamental symptoms in SZ (21, 22). Accessory symptoms were non-specific state phenomena and comprised hallucinations, delusions, and catatonic signs (21). The fundamental symptoms were more specific to SZ and included autism, formal thought disorders, ambivalence, disorders of volition, affective-emotional, and affect-expressive changes (21, 22). Furthermore, when Bleuler (21) described the "autistic core" in SZ patients, he spoke about the withdrawal within the own inner world: "*The most severe schizophrenics, who have no more contact with the outside world live in a world of their own. They have encased themselves with their desires and wishes [. . .]; they have cut themselves off as much as possible from any contact*

with the external world. This detachment from reality with the relative and absolute predominance of the inner life, we term autism" [(21, 23), p. 1122]. In general, the schizophrenic autism is characterized by a rich variety of clinical phenomena such as poor ability to interact with others, inaccessibility, negativistic tendencies, indifference, rigid attitudes, and behaviors, private hierarchy of values and goals, inappropriate expression and behavior, and idiosyncratic logic and thinking, respectively (22). Taken together, from the historical standpoint, SZ, and autism have been regarded as part of the same spectrum (24, 25).

In the early 40s, Kanner's (26) and Asperger's (27) use of the term autism changed it in the direction of its present meaning of disturbed social cognition. Subsequently, with the introduction of DSM-III in the late 1970s, autism became an independent diagnostic entity not being part of the diagnostic concept of SZ. However, problems with interpersonal contact, interaffective attunement, and perspective-taking, are core to both pathologies, though appearing in different forms, and hence, several studies provided empirical evidence for a diagnostic overlap in both disorders (28). Furthermore, clinical studies have shown that negative/deficit, disorganized, and motor symptoms are present in both individuals with autism and patients with SZ (29–31). More recently, before introduction of DSM-5, some authors even discussed an autism dimension for SZ (25). This suggests that distinguishing between both spectrum disorders remains a diagnostic challenge. Such diagnostic overlaps might confound the diagnosis and delay appropriate treatment of these patients. As a matter of fact, the symptoms overlap could at least partially account for the inconsistent findings in previous scientific studies.

Asperger-syndrome (AS) belongs to pervasive developmental disorders and is characterized by interaction and communication difficulties, and repetitive, stereotype, and restricted patterns of behavior. In fact, several clinical studies observed motor abnormalities in individuals with AS including involuntary dyskinesia, rigidity, hypotonia, abnormal posture and gait, clumsiness, reduced coordination of locomotor skills, and unstable balance, respectively (32–35). Some authors even consider motor abnormalities as a putative endophenotype for autism spectrum disorders (36). In the last decade, clinical research interest on motor abnormalities in autism has extended to the investigation of NSS in AS. However, there are only two studies which have investigated NSS prevalence in individuals diagnosed with AS (33, 34) and we are still lacking a profound understanding of NSS in AS.

Overall, the above mentioned clinical studies suggest that motor abnormalities are a typical characteristic of SZ and AS. Hence, there is a stimulating debate whether these disorders share similar sensory-motor features or not (37). Regarding subtle neurological deficits in autism, however, only Mayoral et al. (34) compared NSS in early-onset SZ and AS. Therefore, at present it is difficult to highlight a potential difference in subtle sensory-motor abnormalities in patients with SZ and individuals with AS. The precise evaluation of subtle sensory-motor neurological signs in SZ and AS is of potential clinical significance, since the assessment of NSS might allow for more accurate disease classification. Also, this approach might help to overcome the missing conceptual clarity and better delineate a precise phenotype in order to identify endophenotypes underpinning SZ and AS.

The purpose of this investigation was twofold. First, we were interested in whether there is a difference between NSS severity in patients with SZ and individuals with AS. Second, we sought to identify characteristic NSS, which are either unique or shared by both disorders. Based on the findings of a previous study in juveniles (34) and on our clinical observation, it was hypothesized that individuals with AS would show NSS scores at least as high as patients with SZ. Further, we expected AS individuals being predominantly susceptible to NSS that involve gross motor skills. Finally, we employed a descriptive and predictive linear discrimination analysis (LDA) in order to examine if both total NSS and subscale scores are able to discriminate between the three groups.

MATERIALS AND METHODS

SUBJECTS

The study sample consisted of 26 clinically stable patients with recent-onset SZ, 26 individuals with AS, and 26 healthy controls (HC) who participated in a larger study at the Department of General Psychiatry in Heidelberg, Germany as part of the Toward an Embodied Science of Intersubjectivity-Project (TESIS). The study sample was consecutively recruited between 2010 and 2013 from the Department of General Psychiatry in Heidelberg, Germany and from SALO GmbH in Ludwigshafen, Germany, a professional rehabilitation institution of education for autistic individuals. All participants were Caucasians. Study participants were excluded if: (1) they were aged <18 or >35 years, (2) they had a history of brain trauma or neurological disease, (3) they had a comorbid Axis-I- or -II-Disorder according to ICD-10 or DSM-IV, (4) they had shown alcohol/substance abuse or dependence within 24 months prior to participation, or (5) they had an IQ < 70. Diagnoses of SZ and AS were made by specialized clinicians (DH and PAT) corresponding to DSM-IV criteria and supplemented by an extensive neuropsychological assessment. Clinical symptom determinations and structured clinical diagnostic interviews were conducted by trained clinical raters (Dusan Hirjak, Laura Mehl, and Janna K. Kelbel) and senior diagnosticians (Sabine C. Koch, Philipp Arthur Thomann). In particular, all study individuals were assessed for lifetime psychiatric diagnoses by trained psychiatrists (Dusan Hirjak and Philipp Arthur Thomann) via the German version of the Structured Clinical Interview for DSM-IV (38) and reviews of hospital case notes. All participants in the AS group had previously received a clinical diagnosis of AS (F84.5) from an independent clinician according to standard criteria (a valid diagnosis of autism is an admission criterion for SALO GmbH). In addition, diagnoses of the participants with AS were confirmed with the Autism Diagnostic Observation Schedule [ADOS; (39)] administered by a trained and clinically experienced psychiatrist (Dusan Hirjak). In addition, IQ of individuals with AS (F84.5) has been systematically assessed with the German version of the *Culture Fair Intelligence Test* (CFT-20-R) (40). The intelligence in SZ patients and HC was not explicitly assessed, but clinically judged to be average or above average. Both patients with SZ and HC were required to have a leaving certificate from one of the secondary schools – Hautpschule (9 years), Realschule (10 years), or Gymnasium (13 years) – in order to participate in our study. The demographics and psychiatric history of the two clinical samples were retrieved from medical records. To examine the

possible effect of medications on NSS, we standardized the dosage of antipsychotic medications chlorpromazine equivalents (CPZ). In healthy individuals, we used the PRIME early psychosis screening test [prevention through risk identification, management, and education (PRIME)] to screen for the presence of early psychotic symptoms, including information on any contact or treatment for any mental or psychological disorder (41). All study participants gave informed consent to participation, and the study has been approved by the local ethics committee of the Medical Faculty, University of Heidelberg, Germany.

CLINICAL ASSESSMENTS

Neurological soft signs were assessed using the Heidelberg Scale (2) that consists of five items assessing motor coordination (MOCO) (Ozeretski's test, diadochokinesia, pronation/supination, finger-to-thumb opposition, speech articulation), three items assessing integrative functions (IF) (station and gait, tandem walking, two-point discrimination), two items assessing complex motor tasks (COMT) (finger-to-nose test, fist-edge-palm test), four items assessing right/left and spatial orientation (RLSO) (right/left orientation, graphesthesia, face-hand test, stereognosis), and two items assessing hard signs (HS) (arm holding test, mirror movements). Items were rated on a 0 (no prevalence) to 3 (marked prevalence) point scale. All items, with the exception of station and gait, tandem walking, right/left orientation, speech articulation, primitive reflexes, and Ozeretzki's test were rated separately on the right and left side. A sufficient internal reliability (Cronbach's alpha 0.83) and high test-retest reliability (0.88) have been established previously (2, 42). In the study conducted by Schröder and colleagues (2), to test the interrater reliability of the NSS scale, 42 patients and HC were simultaneously evaluated by two raters. The internal reliability of the scale was assessed by calculating Cronbach's α. The testing procedure was generally standardized, but the explanations and the time required to complete the tasks were adjusted to the condition of the patients. In the present study, the NSS assessment has been conducted by two raters (Janna K. Kelbel and Laura Mehl) trained and supervised by the same psychiatrist (Dusan Hirjak). Both raters were blind to the main hypothesis of the study and investigated study participants independent of their diagnosis. Handedness was assessed on the Edinburgh Inventory (43). The severity of psychopathological symptoms was assessed with the Brief Psychiatric Rating Scale (BPRS) (44), the Scale for the Assessment of Positive Symptoms (SAPS) (45), and the Scale for the Assessment of Negative Symptoms (SANS) (46). Predictors of outcome were rated on the Strauss-Carpenter Scale (SCS) (47). The social, occupational, and psychological functioning in individuals with AS was assessed with the Global Assessment of Functioning (GAF) scale (48).

CHARACTERISTICS OF PARTICIPANTS

The three groups of participants were matched according to age and education. Level of IQ among individuals with AS ranged from 71 to 124 (mean IQ: 99.0 ± 18.5) according to CFT-20-R (40). Patients with SZ according to DSM-IV had an initial onset of psychosis within 2 years prior to study entry with a mean duration of illness of 7.15 months (range 2–15 months). SZ subtypes were distributed as follows: paranoid $n = 12$, disorganized $n = 4$, and undifferentiated $n = 10$. At the time of inclusion, all SZ patients were clinically stable with consistent medication doses for 4 weeks or longer. They were receiving treatment with a single second-generation antipsychotic agent according to their psychiatrists' choice. Patients were treated on average for 2.33 ± 1.44 months throughout the course of illness. Potential extrapyramidal side effects were excluded before study entry by an experienced psychiatrist who was not directly involved in the study. Individuals with AS and HC did not take any antipsychotic, mood stabilizing, anti-cholinergic, or antidepressive medications. SZ patients had low or no prevalence of positive and negative symptoms, as measured by SAPS (range: 0–74), SANS (range: 0–70), and BPRS. At the time of clinical and NSS assessment, no SZ patients manifested psychotic symptoms (two or more of the positive symptom items >3 or a total SAPS score >40).

DATA ANALYSIS

Data were analyzed using the Statistical Package of the Social Sciences (SPSS version 21.0, SPSS Inc., Chicago, IL, USA). Sociodemographic and clinical variables were described and compared between the three groups with unpaired *t-test* or chi-square test for categorical variables using conventional significance levels ($p < 0.05$). To test for differences in NSS performance between the three study subgroups, we conducted an analysis of covariance (ANCOVA) including the potentially distorting factors age, years of education, and CPZ. Gender comparisons on NSS performance within each study group and between the three groups used *t-tests* and analysis of covariance (ANCOVA). Further, p values of the identified NSS subscales were corrected for the number of tested NSS subscales in our main analysis using the Bonferroni method. To this end, α was set to $p = 0.05/N$, where n (=18) equaled the number of correlations (classical Bonferroni correction). For this reason, the corrected threshold was set to $p = 0.0027$ [$\alpha = 0.05/18$ tests (total NSS + five subscale scores × three groups)]. In a second step, a series of ANCOVAs considering age, years of education, and CPZ as covariates was conducted to further examine the differences between groups if a significant main effect was identified. Further, p values of the identified NSS subscales were corrected for the number of tested NSS subscales using the Bonferroni method. To this end, α was set to $p = 0.05/N$, where n (=12) equaled the number of correlations (classical Bonferroni correction). For this reason, the corrected threshold was set to $p = 0.0041$ [$\alpha = 0.05/12$ tests (total NSS + five subscale scores × two groups)]. Correlative analyses of SAPS, SANS, BPRS, and CPZ with total scores and subscores of NSS were conducted with the Pearson correlation coefficient.

To examine the ability of NSS to discriminate among the three groups, both descriptive and predictive LDAs were used (11, 49, 50). The aim of this analysis was to determine whether NSS subscales would discriminate between patients with SZ and those with AS. In this study, total NSS and the five subscale scores were treated as "within subject variable" (independent variables), whereas the diagnostic group was treated as the "between subject factor" (grouping variable). However, only those NSS scores that reached statistical significance in the ANCOVAs were used as predictive variables.

RESULTS

Demographic characteristics of the patient groups and the HC are summarized in **Table 1**. Comparison of the three groups revealed a significant difference in gender (chi-square test: $\chi^2 = 8.35$; df = 2; $p = 0.015$) and CPZ [$F(2, 75) = 85.16$; $p < 0.001$]. There were no significant differences in age [$F(2,75) = 0.55$; $p = 0.577$] and years of education [$F(2, 75) = 2.63$; $p = 0.078$] among the three groups. There was also no significant difference for BPRS scores between SZ patients and individuals with AS [$F(1, 50) = 2.9$; $p = 0.094$]. There were no significant differences between male and female participants in NSS performance among the three groups. In addition, we found no significant differences between male and female individuals in the control group in any of NSS scores (**Table 3**). But, there was a significant gender difference in the performance on NSS subscale COMT in both individuals with AS and SZ patients (**Table 3**). However, this effect is most likely driven by the influence of confounders such as age, education, and medication, since a significant gender effect diminished after covarying for these factors.

GROUP DIFFERENCE IN NSS SCORES (ANCOVA: CONTROLLING FOR AGE, YEARS OF EDUCATION, AND MEDICATION)

Table 1 shows the prevalence of NSS across the three groups. Significant differences after controlling for age, years of education, and CPZ were found in NSS total score [$F(5,72) = 14.7$; $p < 0.001$] and on the five NSS subscales MOCO [$F(5,72) = 11.5$; $p < 0.001$], IF [$F(5,72) = 3.41$; $p = 0.008$], COMT [$F(5,72) = 8.9$; $p < 0.001$], RLSO [$F(5, 72) = 4.02$; $p = 0.003$] and HS [$F(5, 72) = 3.2$; $p = 0.012$] among the three groups (**Figure 1**; **Table 2**). Further, p values of the identified NSS subscales were corrected for the number of tested NSS subscales in our main analysis using the Bonferroni method ($p < 0.0027$). NSS total and two subscale scores (MOCO and COMT) hold Bonferroni correction for multiple testing.

AS VS. SZ

The ANCOVA showed that compared with SZ patients, the individuals with AS showed significantly higher NSS total scores [$F(4, 47) = 3.63$; $p = 0.012$] and higher scores on the subscale COMT [$F(4, 47) = 4.2$; $p = 0.005$]. However, individuals with AS showed lower scores on the NSS subscale MOCO [$F(4, 47) = 4.38$; $p = 0.004$] when compared to SZ patients. Further, p values of the two identified NSS subscales were corrected for the number of tested NSS subscales in our main analysis using the Bonferroni method ($p < 0.0041$). Only the NSS subscale, MOCO hold Bonferroni correction for multiple testing. No significant difference was found between individuals with AS and SZ patients on the

Table 1 | Descriptive summary of the sociodemographic and clinical variables of all participants.

Variable	Asperger-syndrome ($n = 26$)	Schizophrenia ($n = 26$)	Healthy controls ($n = 26$)
Mean age, years (SD)	22.76 ± 3.81	23.38 ± 3.87	23.58 ± 3.77
Gender, *n*			
Male	18 (69.2%)	9 (34.7%)	9 (34.7%)
Female	8 (30.8%)	17 (65.3%)	17 (65.3%)
Handedness, *n*			
Right	23 (88.4%)	26 (100%)	26 (100%)
Left	3 (11.6%)	0 (0%)	0 (0%)
Mean education, years (SD)	12.03 ± 1.84	12.07 ± 1.32	12.8 ± 0.63
Mean duration of illness, months (SD)	–	7.15 ± .31	–
Mean antipsychotic dose(CPZ) (SD)	0	435.11 ± 240.4	0
Mean NSS score (SD)	16.19 ± 6.71 (median = 14.5)	14.92 ± 7.54 (median = 16.0)	5.57 ± 3.08 (median = 5.5)
MOCO	6.23 ± 3.31	6.79 ± 3.91	2.11 ± 1.55
IF	2.61 ± 1.62	1.92 ± 1.38	1.42 ± 1.06
COMT	2.84 ± 1.68	1.61 ± 1.67	0.61 ± 0.89
RLSO	3.07 ± 2.41	1.65 ± 1.89	0.8 ± 1.05
HS	1.42 ± 1.65	1.73 ± 1.34	0.61 ± 0.89
Mean ADOS[a] (SD)	13.61 ± 3.27	–	–
Mean SAPS[b] (SD)	–	20.11 ± 13.98	–
Mean SANS[c] (SD)	41.07 ± 15.78	30.69 ± 18.81	–
Mean BPRS[d] (SD)	29.34 ± 15.49	23.0 ± 10.94	–
Mean SCS[e] (SD)	–	39.0 ± 15.72	–
Mean GAF[f] (SD)	63.96 ± 10.67	–	–

Mean ± standard deviation (SD).

[a] *Autism Diagnostic Observation Schedule.*

[b] *Scale for the assessment of negative symptoms.*

[c] *Scale for the assessment of positive symptoms.*

[d] *Brief Psychiatric Rating Scale.*

[e] *Strauss-Carpenter Scale.*

[f] *Global Assessment of Functioning.*

Table 2 | Group differences in NSS performance.

NSS measure	AS vs. SZ vs. HC		AS vs. SZ		AS vs. HC		SZ vs. HC	
	***F*(5, 72)**	***p***	***F*(4, 47)**	***p***	***F*(3, 48)**	***p***	***F*(4, 47)**	***p***
NSS total score	**14.7**	**<0.001**	3.63	0.012	**24.5**	**<0.001**	**12.9**	**<0.001**
MOCO	**11.5**	**<0.001**	**4.38**	**0.004**	**15.29**	**<0.001**	**11.33**	**<0.001**
COMT	**8.9**	**<0.001**	4.2	0.005	**17.81**	**<0.001**	2.45	0.059
IF	3.41	0.008	2.51	0.054	3.71	0.018	2.59	0.048
RLSO	4.02	0.003	1.5	0.217	**6.21**	**0.001**	1.56	0.2
HS	3.2	0.012	1.1	0.364	3.25	0.03	**4.48**	**0.004**

ANCOVA = controlling for age, years of education and medication (CPZ); MOCO, motor coordination; COMT, complex motor tasks; IF, integrative function; RLSO, right/left and spatial orientation; HS, hard signs; AS, Asperger-syndrome; SZ, schizophrenia patients; HC, healthy controls. Differences surviving Bonferroni correction in bold.

Table 3 | Gender differences in NSS performance (two-tailed *t*-tests).

NSS measures	Asperger-syndrome				Schizophrenia				Healthy controls			
	Male (*n* = 18)	**Female (*n* = 8)**	***t* (df = 24)**	***p***	**Male (*n* = 9)**	**Female (*n* = 17)**	***t* (df = 24)**	***p***	**Male (*n* = 9)**	**Female (*n* = 17)**	***t* (df = 24)**	***p***
NSS total score	16.5 ± 6.86	15.5 ± 6.76	−0.34	0.73	11.66 ± 7.77	16.64 ± 7.04	1.65	0.11	5.88 ± 3.10	5.41 ± 3.16	−0.36	0.71
MOCO	6.55 ± 3.72	5.5 ± 2.13	−0.74	0.46	5.44 ± 4.15	7.47 ± 3.71	1.27	0.21	2.11 ± 1.69	2.11 ± 1.53	0.01	0.99
COMT	3.27 ± 1.70	1.87 ± 1.14	−2.08	**0.04**	0.66 ± 1.65	2.11 ± 1.49	2.26	**0.03**	0.66 ± 1.0	0.58 ± 087	−0.2	0.83
IF	2.50 ± 1.72	2.87 ± 1.45	0.53	0.59	1.55 ± 1.01	2.11 ± 1.53	0.98	0.33	1.66 ± 1.11	1.29 ± 1.04	−0.84	0.40
RLSO	2.77 ± 1.80	3.75 ± 3.49	0.94	0.35	1.44 ± 1.87	1.76 ± 1.95	0.4	0.69	0.55 ± 0.88	0.94 ± 1.14	0.87	0.38
HS	1.38 ± 1.81	1.50 ± 1.30	0.15	0.87	1.33 ± 1.0	1.94 ± 1.47	1.1	0.28	0.88 ± 1.16	0.47 ± 0.71	−1.13	0.26

Mean ± SD; MOCO, motor coordination; COMT, complex motor tasks; IF, integrative function; RLSO, right/left and spatial orientation; HS, hard. Bold font indicates significant differences ($p < 0.05$).

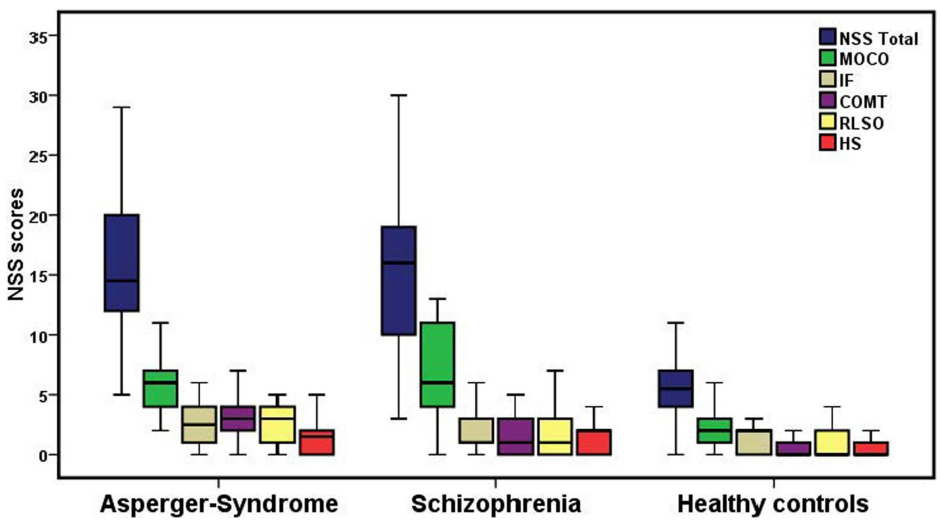


FIGURE 1 | Neurological soft signs total scores and NSS scores on the five subscales among the three groups. The bottom and top of the box represent the first and third quartile, and the band inside the box is the second quartile (the median). The ends of the whiskers indicate the minimum and maximum of the NSS performance. MOCO, motor coordination; COMT, complex motor tasks; IF, integrative functions; RLSO, right/left and spatial orientation; HS, hard signs.

subscales IF [$F(4, 47) = 2.51$; $p = 0.054$], RLSO [$F(4, 47) = 1.5$; $p = 0.217$], and HS [$F(4, 47) = 1.1$; $p = 0.364$].

AS VS. HC

Compared with HC, individuals with AS showed significantly higher NSS total scores [$F(3, 48) = 24.50$; $p < 0.001$] and elevated NSS on the subscales MOCO [$F(3, 48) = 15.29$; $p < 0.001$], IF [$F(3, 48) = 3.71$; $p = 0.018$], COMT [$F(3, 48) = 17.81$; $p < 0.001$], RLSO [$F(3, 48) = 6.21$; $p = 0.001$], and HS [$F(3, 48) = 3.25$; $p = 0.03$]. NSS total and three subscale scores (MOCO, COMT, and RLSO) hold Bonferroni correction for multiple testing ($p < 0.0041$).

SZ VS. HC

Compared with HC, SZ patients showed significantly more total NSS signs [$F(4, 47) = 12.90$; $p < 0.001$] and higher NSS scores on the subscale MOCO [$F(4, 47) = 11.33$; $p < 0.001$], IF [$F(4, 47) = 2.59$; $p = 0.048$], and HS [$F(4, 47) = 4.48$; $p = 0.004$]. NSS total and two subscale scores (MOCO and HS) hold Bonferroni correction for multiple testing ($p < 0.0041$). Additionally, no significant difference was found between SZ patients and HC on the subscale COMT [$F(4, 47) = 2.45$; $p = 0.059$] and RLSO [$F(4, 47) = 1.56$; $p = 0.2$].

CLINICAL COMPARISONS

In patients with SZ, SAPS, SANS, and BPRS scores were not significantly associated with total score and five subscores of NSS at the conventional significance level ($p < 0.05$). In individuals with AS, BPRS scores were not associated with total score and five subscores of NSS at the conventional significance level ($p < 0.05$).

DISCRIMINANT ANALYSES OF NSS PERFORMANCE

In this study, we conducted a LDA (11, 49, 50), to examine the ability of the total NSS and five subscale scores to discriminate between the three groups. With this method, we also tested for the possibility of predicting the correct diagnosis solely based on NSS performance. Only the NSS subscales that reached statistical significance in *post hoc* analysis and survived the Bonferroni correction were used as predictive variables.

Using predictive LDA, we found that 71.8% of the cases were correctly classified in terms of the group as a function of the total NSS and two subscale scores (MOCO and COMT). The individual discriminant rates for each diagnostic group were 92.3% for HC, 69.2% for individuals with AS, and 53.8% for SZ patients. The results of the descriptive LDA revealed the emergence of two significant linear discriminant functions: function 1 (Wilks' $\lambda = 0.495$; $\chi^2 = 52.106$; $p < 0.001$; eigenvalue: 0.627; canonical correlation = 0.621) could explain 72.1% of the variance, while function 2 (Wilks' $\lambda = 0.805$; $\chi^2 = 16.084$; $p < 0.001$; eigenvalue: 0.243; canonical correlation = 0.442) could only explain 27.9% of the variance. The distribution of the three groups is shown in **Figure 2** and function 1 and function 2 are illustrated.

In this study, predictive LDA was also conducted for group–group comparison. All three analyses showed significant results.

AS VS. SZ

One of them was between individuals with AS and SZ patients. In this analysis, only the NSS subscale MOCO that reached statistical significance in the *post hoc* analysis and survived the Bonferroni correction was used as predictor variable. The total correct discriminant rate was 61.5%. The results of the descriptive LDA revealed the emergence of non-significant linear discriminant function (Wilks' $\lambda = 0.994$; $\chi^2 = 0.283$; $p = 0.595$; eigenvalue: 0.006; canonical correlation = 0.076). Because of the non-significant discriminant function between individuals with AS and patients with SZ, we re-ran the LDA by adding two more NSS variables, which did not survive the Bonferroni correction (11). After including the NSS total score and the NSS subscale COMT in the LDA, the correct discriminant rate elevated from 61.5 to 71.2% (Wilks' $\lambda = 0.774$; $\chi^2 = 12.438$; $p = 0.006$; eigenvalue: 0.292; canonical correlation = 0.476). The correct rate of AS individuals was 65.4%, while the correct rate of SZ patients was 76.9%.

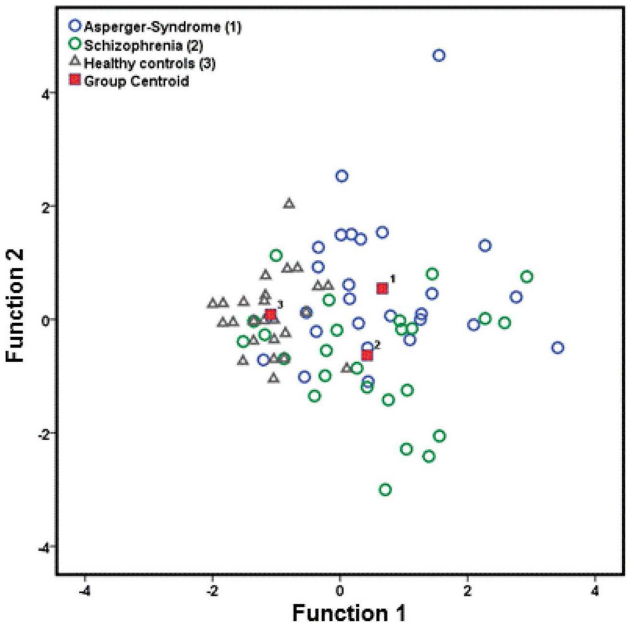


FIGURE 2 | Canonical discriminant functions of neurological soft signs (total score, MOCO, and COMT), which are prevalence for patients with AS, schizophrenia, and healthy controls. MOCO, motor coordination; COMT, complex motor tasks.

AS VS. HC

The other was between individuals with AS and HC. In this analysis, total NSS and three subscale scores (MOCO, COMT, and HS) that reached statistical significance in the *post hoc* analysis and survived the Bonferroni correction were used as predictor variables. The total correct discriminant rate was 92.3%. The descriptive LDA revealed the emergence of one significant linear discriminant function (Wilks' $\lambda = 0.445$; $\chi^2 = 37.746$; $p < 0.001$; eigenvalue: 1.195; canonical correlation = 0.738).

SZ VS. HC

The remaining predictive LDA was between SZ patients and HC. In this analysis, total NSS and three subscale scores (MOCO and HS) that reached statistical significance in the *post hoc* analysis and survived the Bonferroni correction were used as predictor variables.

The total correct discriminant rate was 80.8%. The results of the descriptive LDA revealed the emergence of one significant linear discriminant function (Wilks' $\lambda = 0.569$; $\chi^2 = 27.334$; $p < 0.001$; eigenvalue: 0.757; canonical correlation = 0.656).

POTENTIAL INFLUENCE OF MEDICATION

In patients with SZ, NSS total scores ($r = 0.335$; $p = 0.095$) and scores on the subscales MOCO ($r = 0.262$; $p = 0.228$), COMT ($r = 0.133$; $p = 0.547$), HS ($r = 0.255$; $p = 0.240$), IF ($r = 0.289$; $p = 0.182$), and RLSO ($r = 0.140$; $p = 0.523$) were not associated with CPZ equivalents at the conventional significance level ($p < 0.05$).

DISCUSSION

This study assessed and compared NSS levels in both patients with SZ and AS. Two main findings emerged: first, patients with SZ show significantly higher NSS score on the subscale MOCO when compared to individuals with AS. Second, SZ patients can be distinguished from those with AS by only one NSS subscale (MOCO). These findings were consistent across the analyses of prevalence and in the LDA.

Previous studies on motor abnormalities in AS clearly underestimated the prevalence of NSS in this syndrome and focused exclusively on rather complex movement disorders. In fact, only two previous studies investigated the severity of NSS in AS (33, 34). In the study conducted by Tani (33), individuals with AS had significantly higher NSS total and complex motor acts scores when compared to the control group. The authors concluded that NSS represent a non-specific vulnerability factor for AS (33). More recently, Mayoral (34) investigated 30 patients with early-onset SZ and 29 individuals with AS. In agreement with our results, they found that individuals with AS have higher NSS scores than HC. Second, however, the authors concluded that there are no significant differences between both patient groups in any of the NSS scores. However, it is possible that the discordant findings reported by Mayoral (34) were due to large differences in sociodemographic variables among the study participants. In fact, the IQ levels in the control group were significantly higher than in SZ patients and individuals with AS. Hence, some patients with AS were taking antipsychotic medication, a fact that may have biased particular NSS tasks in this group. Last but not least, recent research indicates that only 5% of SZ patients have a psychosis onset before age of 15 years (51). Therefore, investigating young patients with early-onset SZ does not allow making inferences for the whole SZ spectrum, because NSS might be instable in subgroups of young patients with incomplete brain maturation. Thus, the above mentioned findings cannot be generalized to the whole autism spectrum.

To some extent, our findings are consistent with the two above mentioned NSS studies. In line with results presented by Tani (33), we found that individuals with AS exhibit higher NSS levels on the subscale MOCO, COMT, and RLSO when compared to HC. However, we did not find any significant difference between NSS levels on the subscale HS. In contrast to Mayoral (34), who found no differences between SZ and patients with AS, we observed significantly higher NSS scores on the subscale MOCO in SZ when compared to individuals with AS. Compared with both previous studies, our findings are likely to be more robust because of three reasons: first, individuals with AS were free of psychotropic medication. Though all our SZ patients were medicated, the negative results in correlations between NSS and CPZ further reduces potential concerns that our findings might be confounded by antipsychotic drug treatment. Furthermore, the duration of exposure to second-generation antipsychotic medication in SZ patients was rather low. A second strength of our study is that individuals with SZ and AS had low prevalence of acute psychiatric symptoms and, in addition, did not differ in BPRS scores as measures of psychopathology. We believe this to be important, as SZ patients with more severe psychotic symptoms have been shown to score higher on the NSS scale in comparison with SZ patients without any negative or positive symptoms (3). In fact, recent studies showed that patients with negative symptoms are characterized by more severe neurological abnormalities including different sensory-motor functions (52). For instance, a number of reports have also noted that SZ patients with negative symptoms exhibit higher prevalence of spontaneous movements (53, 54) or NSS (55–59) . In conclusion, there is an association between NSS and negative symptoms in SZ. However, our SZ sample scored rather low on SANS and SAPS. Third, SZ patients and individuals with AS were of similar educational level. Given the large body of evidence in individuals with AS and SZ suggesting a significant relationship between intelligence and movement (60), we used years of education as a covariate when analyzing differences in NSS scores. In contrast to both aforementioned studies, our study sample comprised mainly young adults in a clinically stable disease state and rather advanced brain maturation. However, for the interpretation of the present results, it is important to bear in mind that the human brain undergoes a highly dynamic development, which continues into adulthood (61). While the majority of longitudinal studies on brain growth in autism focused on children, the trend of brain development in adolescence, and adulthood remains unidentified (62). Our data might support the hypothesis of developmental deficits in AS during adolescence and adulthood.

Several lines of scientific evidence suggest that AS and SZ have both unique and similar sensory-motor features. In particular, there is a stimulating debate whether these disorders are related conditions or not (37). The findings of our present study provide support for both positions. SZ patients exhibited significantly higher NSS levels on the subscale MOCO when compared to individuals with AS. The NSS subscale MOCO comprises both, tasks which involve small muscles of the hand, and tasks which necessitate a tight link between one's own bodily movement and the spatial–temporal constraints. This finding is of particular interest given recent evidence of individuals with SZ showing poor levels of motor dexterity (63). As such, this action is based on visual perception and fine motor precision. Therefore, our first finding supports the hypothesis that patients with SZ exhibit serious problems when using sensory information to guide and time fine finger and hand movements. Moreover, there is some evidence that abnormalities of fine MOCO have a developmental origin and manifest even in a group of clinical at-risk mental state individuals (64, 65). In fact, research on NSS in ultra-high risk (UHR) conditions for developing mental illness might also provide important clues for the understanding of motor abnormalities in

psychotic disorders. Nevertheless, to date, only few studies investigated NSS in UHR individuals (66, 67). Leask and colleagues (67) concluded that NSS might precede SZ, but are not caused by infectious illness in early childhood. In the pioneer longitudinal neuroimaging study on UHR individuals, Mittal and colleagues (68) suggested a significant relationship between NSS and longitudinal cerebellar-thalamic tract integrity. As such, NSS might provide insight into the role of cognitive dysmetria in the high-risk period. These results are supported by previous research on infant motor development that considered childhood neuromotor dysfunction as a risk factor for SZ spectrum disorders (64, 69). In summary, NSS might be considered as an intrinsic part of vulnerability to psychosis and should be discussed as markers of disordered neurodevelopment in SZ (70).

After Bonferroni correction, no significant differences were found between SZ and AS in total NSS and four subscales comprising rather gross motor skills such as stait and gait, tandem walking, finger-to-nose test or right/left orientation. There are several explanations for the particular deficit in gross motor skills in both disorders. In order to properly perform gross bodily actions, the interaction of motor cortex, basal ganglia, and thalamus is critical. Recently, altered gray matter volumes within the limbic basal ganglia loop system (e.g., left thalamus, putamen) were found to be common in both SZ and autism (37, 71). We believe that these findings lend support to the theory of a disrupted basal ganglia loop system in both disorders and suggest that SZ and AS share a number of neurobiological similarities. Hence, our results provide arguments against the theory that SZ and AS are diametrically opposite ends of a continuum (72).

The present study employed LDA in order to test for unique disease related patterns of NSS and to explore the degree of accuracy to which these patterns could be used to statistically discriminate between SZ and AS. Although the NSS subscale MOCO was found to be the most important predictor involved in discriminating, among the two clinical groups, it only accounted for an overall 61.5% correct classification. These results implicate that the level of abnormalities in perception-action coupling as described by MOCO may serve as a valuable predictor when trying to differentiate between patients with SZ and AS. However, it is noteworthy that by combining the NSS subscale MOCO with the total NSS and COMT subscale score the correct discriminant rate elevated to 71.2% and revealed significant discriminant function. Because of our modest sample size, some findings diminished more than it would have probably been the case with a larger study group. Although the LDA consisting NSS total scores was significant, NSS subscales tended to fall below our cut-off of 0.05 as the determinant of significance. Still, our observation that the subscale MOCO has a significant discriminant power between SZ patients and individuals with AS supports earlier assumptions that abnormalities of motor dexterity *per se* might be a major characteristic of SZ (73). According to our results, especially motor tests evaluating fine motor skills and manual dexterity might be helpful when classifying and differentiating patients with SZ and individuals with AS.

LIMITATIONS

We acknowledge several potential limitations of this study such as the possible differences in IQ levels among the study participants. It is thus possible that we missed small between-group effects due to missing IQ scores in SZ patients and the control group. Apart from this, deficits in global measures of cognition such as intelligence are common in SZ patients (74, 75). On the other side, it is a well-established finding that IQ levels do not change over the course of illness and that lower IQ is a stable trait in patients suffering from SZ (76–78). Furthermore, variables such as education, occupation, and age can contribute significantly to IQ values (79). In other words, we believe the recent evidence to clearly suggest years of education as being an appropriate and stable indicator of global cognition in SZ. Second, the relatively small number of participants in each study group limits the power of the LDA. Third, statistical analysis of the three groups revealed a significant difference in gender. According to Cai (80) and colleagues, higher NSS levels were observed in 14- and 15-years-old boys when compared with girls of the same age. Since the differences in NSS performance declined with increasing age, the authors concluded that young boys might experience a delay of brain maturation when compared to girls of similar age, and hence, this might cause higher NSS scores in the male group (80). In our study, there were no differences for age distribution among the three groups and the majority of our study subjects were young adults with completed brain maturation. Further, there were no significant differences between male and female participants in NSS performance among the three groups. Therefore, uneven gender distribution across diagnostic groups might have not directly impact upon results of the statistical analysis in this study. Fourth, all SZ patients had been exposed to antipsychotic medication. In order to partial out a putative dose-dependent effect of second-generation antipsychotics on NSS performance, SZ patients' CPZ were considered as potential confounders in the present study. Although CPZ doses were included as covariates in the statistical analyses, we cannot completely rule out the possibility that antipsychotic medication might have influenced the NSS performance to some degree. Still, an influence of medication in our study is unlikely as every SZ patient was treated with atypical neuroleptics, the duration of treatment was relatively short, and none of the subjects showed serious medication side effects. Furthermore, none of the individuals with AS was treated with second- or first-generation antipsychotics. Correspondingly, second-generation antipsychotic treatment or medication side effects seem to have no effect on NSS performance in SZ (81). Fifth, healthy participants were not explicitly screened for AS by means of a standardized test. However, no signs of autistic traits were observed in healthy subjects during clinical and diagnostic (DSM-IV) interviewing. Last but not least, our study sample comprised patients suffering from different subtypes of SZ, a point that might complicate the interpretation of our results (82). However, subgroups were too small to test for this potential influence. Moreover, it is important to bear in mind that our findings are preliminary and that they need to be replicated in larger samples.

CONCLUSION

Sensory-motor abnormalities in SZ and AS might manifest as NSS. Since NSS are present in both, individuals with SZ and AS, they may represent a putative neuromotor marker across the traditional diagnostic categorization. Understanding the role of NSS could

help to gain further insight into the neurobiological underpinnings of SZ and AS. To this end, future studies should ideally combine thorough clinical, neurological, and psychopathological assessments with multi-modal neuroimaging techniques in order to elucidate how the respective factors relate to each other.

AUTHOR CONTRIBUTIONS

Dusan Hirjak, Philipp Arthur Thomann, Sabine C. Koch, and Thomas Fuchs designed the study and were involved in the interpretation of the results. Dusan Hirjak, Robert Christian Wolf, Katharina Maria Kubera, and Tanja Traeger performed statistical analyses. Dusan Hirjak, Philipp Arthur Thomann, Laura Mehl, and Janna K. Kelbel undertook neurological, psychopathological and psychometric assessments. Dusan Hirjak, Philipp Arthur Thomann, Katharina Maria Kubera and Robert Christian Wolf wrote the manuscript. All authors contributed to and have approved the final manuscript.

ACKNOWLEDGMENTS

The authors cordially thank all patients and healthy controls for participating in this study. This work was supported by the Marie-Curie Initial Training Network TESIS: "Toward an Embodied Science of InterSubjectivity" (FP7-PEOPLE-2010-ITN, 264828). We also acknowledge financial support by Deutsche Forschungsgemeinschaft (DFG) and University of Heidelberg within the funding program "Open Access Publishing".

REFERENCES

1. Heinrichs DW, Buchanan RW. Significance and meaning of neurological signs in schizophrenia. *Am J Psychiatry* (1988) **145**:11–8.
2. Schroder J, Niethammer R, Geider FJ, Reitz C, Binkert M, Jauss M, et al. Neurological soft signs in schizophrenia. *Schizophr Res* (1991) **6**:25–30. doi:10.1016/0920-9964(91)90017-L
3. Jahn T, Hubmann W, Karr M, Mohr F, Schlenker R, Heidenreich T, et al. Motoric neurological soft signs and psychopathological symptoms in schizophrenic psychoses. *Psychiatry Res* (2006) **142**:191–9. doi:10.1016/j.psychres.2002.12.003
4. Chan RC, Xu T, Heinrichs RW, Yu Y, Wang Y. Neurological soft signs in schizophrenia: a meta-analysis. *Schizophr Bull* (2010) **36**:1089–104. doi:10.1093/schbul/sbp011
5. Bombin I, Arango C, Buchanan RW. Significance and meaning of neurological signs in schizophrenia: two decades later. *Schizophr Bull* (2005) **31**:962–77. doi:10.1093/schbul/sbi028
6. Bolton D, Gibb W, Lees A, Raven P, Gray JA, Chen E, et al. Neurological soft signs in obsessive compulsive disorder: standardised assessment and comparison with schizophrenia. *Behav Neurol* (1998) **11**:197–204. doi:10.1155/1999/639045
7. Jaafari N, Baup N, Bourdel MC, Olie JP, Rotge JY, Wassouf I, et al. Neurological soft signs in OCD patients with early age at onset, versus patients with schizophrenia and healthy subjects. *J Neuropsychiatry Clin Neurosci* (2011) **23**:409–16. doi:10.1176/appi.neuropsych.23.4.409
8. Mohr F, Hubmann W, Cohen R, Bender W, Haslacher C, Honicke S, et al. Neurological soft signs in schizophrenia: assessment and correlates. *Eur Arch Psychiatry Clin Neurosci* (1996) **246**:240–8. doi:10.1007/BF02190275
9. Kinney DK, Yurgelun-Todd DA, Woods BT. Neurologic signs of cerebellar and cortical sensory dysfunction in schizophrenics and their relatives. *Schizophr Res* (1999) **35**:99–104. doi:10.1016/S0920-9964(98)00121-2
10. Rigucci S, Dimitri-Valente G, Mandarelli G, Manfredi G, Comparelli A, Filippis SD, et al. Neurological soft signs discriminate schizophrenia from bipolar disorder. *J Psychiatr Pract* (2014) **20**:147–53. doi:10.1097/01.pra.0000445250.20875.0e
11. Zhao Q, Ma YT, Lui SS, Liu WH, Xu T, Yu X, et al. Neurological soft signs discriminate schizophrenia from major depression but not bipolar disorder. *Prog Neuropsychopharmacol Biol Psychiatry* (2013) **43**:72–8. doi:10.1016/j.pnpbp.2012.12.006
12. Krebs MO, Gut-Fayand A, Bourdel M, Dischamp J, Olie J. Validation and factorial structure of a standardized neurological examination assessing neurological soft signs in schizophrenia. *Schizophr Res* (2000) **45**:245–60. doi:10.1016/S0920-9964(99)00206-6
13. Thomann PA, Wustenberg T, Santos VD, Bachmann S, Essig M, Schroder J. Neurological soft signs and brain morphology in first-episode schizophrenia. *Psychol Med* (2009) **39**:371–9. doi:10.1017/S0033291708003656
14. Hirjak D, Wolf RC, Stieltjes B, Hauser T, Seidl U, Schroder J, et al. Cortical signature of neurological soft signs in recent onset schizophrenia. *Brain Topogr* (2014) **27**:296–306. doi:10.1007/s10548-013-0292-z
15. Zhao Q, Li Z, Huang J, Yan C, Dazzan P, Pantelis C, et al. Neurological soft signs are not "soft" in brain structure and functional networks: evidence from ALE meta-analysis. *Schizophr Bull* (2014) **40**:626–41. doi:10.1093/schbul/sbt063
16. Dazzan P, Morgan KD, Orr KG, Hutchinson G, Chitnis X, Suckling J, et al. The structural brain correlates of neurological soft signs in AESOP first-episode psychoses study. *Brain* (2004) **127**:143–53. doi:10.1093/brain/awh015
17. Janssen J, Diaz-Caneja A, Reig S, Bombin I, Mayoral M, Parellada M, et al. Brain morphology and neurological soft signs in adolescents with first-episode psychosis. *Br J Psychiatry* (2009) **195**:227–33. doi:10.1192/bjp.bp.108.052738
18. Thomann PA, Roebel M, Dos Santos V, Bachmann S, Essig M, Schroder J. Cerebellar substructures and neurological soft signs in first-episode schizophrenia. *Psychiatry Res* (2009) **173**:83–7. doi:10.1016/j.pscychresns.2008.07.006
19. Hirjak D, Wolf RC, Stieltjes B, Seidl U, Schroder J, Thomann PA. Neurological soft signs and subcortical brain morphology in recent onset schizophrenia. *J Psychiatr Res* (2012) **46**:533–9. doi:10.1016/j.jpsychires.2012.01.015
20. Hirjak D, Wolf RC, Stieltjes B, Hauser T, Seidl U, Thiemann U, et al. Neurological soft signs and brainstem morphology in first-episode schizophrenia. *Neuropsychobiology* (2013) **68**:91–9. doi:10.1159/000350999
21. Bleuler E. *Dementia Praecox or the Group of Schizophrenias. Zinkin J, Trans.* New York, NY: International Universities Press (1950).
22. Parnas J. The core Gestalt of schizophrenia. *World Psychiatry* (2012) **11**:67–9. doi:10.1016/j.wpsyc.2012.05.002
23. Parnas J. A disappearing heritage: the clinical core of schizophrenia. *Schizophr Bull* (2011) **37**:1121–30. doi:10.1093/schbul/sbr081
24. Cappon D. Clinical manifestations of autism and schizophrenia in childhood. *Can Med Assoc J* (1953) **69**:44–9.
25. Pelletier AL, Mittal VA. An autism dimension for schizophrenia in the next Diagnostic and Statistical Manual? *Schizophr Res* (2012) **137**:269–70. doi:10.1016/j.schres.2012.01.033
26. Kanner L. Early infantile autism. *J Pediatr* (1944) **25**:211–7. doi:10.1016/S0022-3476(44)80156-1
27. Asperger H. Die "Autistischen Psychopathen" im kindesalter. *Arch Psychiatr Nervenkr* (1944) **117**:76–136. doi:10.1007/BF01837709
28. Barneveld PS, Pieterse J, De Sonneville L, Van Rijn S, Lahuis B, Van Engeland H, et al. Overlap of autistic and schizotypal traits in adolescents with Autism Spectrum Disorders. *Schizophr Res* (2011) **126**:231–6. doi:10.1016/j.schres.2010.09.004
29. Konstantareas MM, Hewitt T. Autistic disorder and schizophrenia: diagnostic overlaps. *J Autism Dev Disord* (2001) **31**:19–28. doi:10.1023/A:1005605528309
30. Bevan Jones R, Thapar A, Lewis G, Zammit S. The association between early autistic traits and psychotic experiences in adolescence. *Schizophr Res* (2012) **135**:164–9. doi:10.1016/j.schres.2011.11.037
31. Waris P, Lindberg N, Kettunen K, Tani P. The relationship between Asperger's syndrome and schizophrenia in adolescence. *Eur Child Adolesc Psychiatry* (2013) **22**:217–23. doi:10.1007/s00787-012-0338-x
32. Rinehart NJ, Tonge BJ, Bradshaw JL, Iansek R, Enticott PG, Mcginley J. Gait function in high-functioning autism and Asperger's disorder: evidence for basal-ganglia and cerebellar involvement? *Eur Child Adolesc Psychiatry* (2006) **15**:256–64. doi:10.1007/s00787-006-0530-y
33. Tani P, Lindberg N, Appelberg B, Nieminen-Von Wendt T, Von Wendt L, Porkka-Heiskanen T. Clinical neurological abnormalities in young adults with Asperger syndrome. *Psychiatry Clin Neurosci* (2006) **60**:253–5. doi:10.1111/j.1440-1819.2006.01494.x
34. Mayoral M, Merchan-Naranjo J, Rapado M, Leiva M, Moreno C, Giraldez M, et al. Neurological soft signs in juvenile patients with Asperger syndrome, early-onset psychosis, and healthy controls. *Early Interv Psychiatry* (2010) **4**:283–90. doi:10.1111/j.1751-7893.2010.00197.x
35. Whyatt C, Craig C. Sensory-motor problems in Autism. *Front Integr Neurosci* (2013) **7**:51. doi:10.3389/fnint.2013.00051

36. Esposito G, Pasca SP. Motor abnormalities as a putative endophenotype for Autism Spectrum Disorders. *Front Integr Neurosci* (2013) **7**:43. doi:10.3389/fnint.2013.00043
37. Cheung C, Yu K, Fung G, Leung M, Wong C, Li Q, et al. Autistic disorders and schizophrenia: related or remote? An anatomical likelihood estimation. *PLoS One* (2010) **5**:e12233. doi:10.1371/journal.pone.0012233
38. Wittchen HU, Wunderlich U, Gruschwitz S, Zaudig M. *SKID-I: Strukturiertes Klinisches Interview für DSM-IV*. Göttingen: Hogrefe (1997).
39. Lord C, Rutter M, Goode S, Heemsbergen J, Jordan H, Mawhood L, et al. Autism diagnostic observation schedule: a standardized observation of communicative and social behavior. *J Autism Dev Disord* (1989) **19**:185–212. doi:10.1007/BF02211841
40. Weiß RH, editor. *CFT 20-R Grundintelligenztest Skala 2 – Revision*. Göttingen: Hogrefe (2006).
41. Miller TJ, Mcglashan TH, Rosen JL, Cadenhead K, Cannon T, Ventura J, et al. Prodromal assessment with the structured interview for prodromal syndromes and the scale of prodromal symptoms: predictive validity, interrater reliability, and training to reliability. *Schizophr Bull* (2003) **29**:703–15. doi:10.1093/oxfordjournals.schbul.a007040
42. Bachmann S, Bottmer C, Schroder J. Neurological soft signs in first-episode schizophrenia: a follow-up study. *Am J Psychiatry* (2005) **162**:2337–43. doi:10.1176/appi.ajp.162.12.2337
43. Oldfield RC. The assessment and analysis of handedness: the Edinburgh inventory. *Neuropsychologia* (1971) **9**:97–113. doi:10.1016/0028-3932(71)90067-4
44. Overall JE, Gorham DR. The brief psychiatric rating scale. *Psychol Rep* (1962) **10**:799–812. doi:10.2466/pr0.1962.10.3.799
45. Andreasen NC. *The Scale for the Assessment of Positive Symptoms (SAPS)*. Iowa City: University of Iowa (1984).
46. Andreasen NC. *The Scale for the Assessment of Negative Symptoms (SANS)*. Iowa City: University of Iowa (1983).
47. Strauss JS, Carpenter WT Jr. The prediction of outcome in schizophrenia. II. Relationships between predictor and outcome variables: a report from the WHO international pilot study of schizophrenia. *Arch Gen Psychiatry* (1974) **31**:37–42. doi:10.1001/archpsyc.1974.01760130021003
48. Hall RC. Global assessment of functioning. A modified scale. *Psychosomatics* (1995) **36**:267–75. doi:10.1016/S0033-3182(95)71656-5
49. Fisher RA. The use of multiple measurements in taxonomic problems. *Ann Hum Genet* (1936) **7**:179–88.
50. Arango C, Bartko JJ, Gold JM, Buchanan RW. Prediction of neuropsychological performance by neurological signs in schizophrenia. *Am J Psychiatry* (1999) **156**:1349–57.
51. Pakyurek M, Yarnal R, Carter C. Treatment of psychosis in children and adolescents: a review. *Adolesc Med State Art Rev* (2013) **24**:420–32, ix.
52. Galderisi S, Maj M. Deficit schizophrenia: an overview of clinical, biological and treatment aspects. *Eur Psychiatry* (2009) **24**:493–500. doi:10.1016/j.eurpsy.2009.03.001
53. Chen EY, Lam LC, Chen RY, Nguyen DG. Negative symptoms, neurological signs and neuropsychological impairments in 204 Hong Kong Chinese patients with schizophrenia. *Br J Psychiatry* (1996) **168**:227–33. doi:10.1192/bjp.168.2.227
54. Telfer S, Shivashankar S, Krishnadas R, Mccreadie RG, Kirkpatrick B. Tardive dyskinesia and deficit schizophrenia. *Acta Psychiatr Scand* (2011) **124**:357–62. doi:10.1111/j.1600-0447.2011.01751.x
55. Buchanan RW, Kirkpatrick B, Heinrichs DW, Carpenter WT Jr. Clinical correlates of the deficit syndrome of schizophrenia. *Am J Psychiatry* (1990) **147**:290–4.
56. Galderisi S, Maj M, Mucci A, Cassano GB, Invernizzi G, Rossi A, et al. Historical, psychopathological, neurological, and neuropsychological aspects of deficit schizophrenia: a multicenter study. *Am J Psychiatry* (2002) **159**:983–90. doi:10.1176/appi.ajp.159.6.983
57. Peralta V, Moreno-Izco L, Sanchez-Torres A, Garcia De Jalon E, Campos MS, Cuesta MJ. Characterization of the deficit syndrome in drug-naive schizophrenia patients: the role of spontaneous movement disorders and neurological soft signs. *Schizophr Bull* (2014) **40**:214–24. doi:10.1093/schbul/sbs152
58. Buchanan RW, Breier A, Kirkpatrick B, Elkashef A, Munson RC, Gellad F, et al. Structural abnormalities in deficit and nondeficit schizophrenia. *Am J Psychiatry* (1993) **150**:59–65.
59. Arango C, Kirkpatrick B, Buchanan RW. Neurological signs and the heterogeneity of schizophrenia. *Am J Psychiatry* (2000) **157**:560–5. doi:10.1176/appi.ajp.157.4.560
60. Dziuk MA, Gidley Larson JC, Apostu A, Mahone EM, Denckla MB, Mostofsky SH. Dyspraxia in autism: association with motor, social, and communicative deficits. *Dev Med Child Neurol* (2007) **49**:734–9. doi:10.1111/j.1469-8749.2007.00734.x
61. Giedd JN, Blumenthal J, Jeffries NO, Castellanos FX, Liu H, Zijdenbos A, et al. Brain development during childhood and adolescence: a longitudinal MRI study. *Nat Neurosci* (1999) **2**:861–3. doi:10.1038/13158
62. Hua X, Thompson PM, Leow AD, Madsen SK, Caplan R, Alger JR, et al. Brain growth rate abnormalities visualized in adolescents with autism. *Hum Brain Mapp* (2013) **34**:425–36. doi:10.1002/hbm.21441
63. Sasayama D, Hori H, Teraishi T, Hattori K, Ota M, Matsuo J, et al. Benzodiazepines, benzodiazepine-like drugs, and typical antipsychotics impair manual dexterity in patients with schizophrenia. *J Psychiatr Res* (2014) **49**:37–42. doi:10.1016/j.jpsychires.2013.10.019
64. Cannon M, Jones P, Huttunen MO, Tanskanen A, Huttunen T, Rabe-Hesketh S, et al. School performance in Finnish children and later development of schizophrenia: a population-based longitudinal study. *Arch Gen Psychiatry* (1999) **56**:457–63. doi:10.1001/archpsyc.56.5.457
65. Tamagni C, Studerus E, Gschwandtner U, Aston J, Borgwardt S, Riecher-Rossler A. Are neurological soft signs pre-existing markers in individuals with an at-risk mental state for psychosis? *Psychiatry Res* (2013) **210**:427–31. doi:10.1016/j.psychres.2013.06.016
66. McGorry PD, Mcfarlane C, Patton GC, Bell R, Hibbert ME, Jackson HJ, et al. The prevalence of prodromal features of schizophrenia in adolescence: a preliminary survey. *Acta Psychiatr Scand* (1995) **92**:241–9. doi:10.1111/j.1600-0447.1995.tb09577.x
67. Leask SJ, Done DJ, Crow TJ. Adult psychosis, common childhood infections and neurological soft signs in a national birth cohort. *Br J Psychiatry* (2002) **181**:387–92. doi:10.1192/bjp.181.5.387
68. Mittal VA, Dean DJ, Bernard JA, Orr JM, Pelletier-Baldelli A, Carol EE, et al. Neurological soft signs predict abnormal cerebellar-thalamic tract development and negative symptoms in adolescents at high risk for psychosis: a longitudinal perspective. *Schizophr Bull* (2014). doi:10.1093/schbul/sbt199
69. Murray GK, Jones PB, Moilanen K, Veijola J, Miettunen J, Cannon TD, et al. Infant motor development and adult cognitive functions in schizophrenia. *Schizophr Res* (2006) **81**:65–74. doi:10.1016/j.schres.2005.08.016
70. Dazzan P, Murray RM. Neurological soft signs in first-episode psychosis: a systematic review. *Br J Psychiatry Suppl* (2002) **43**:s50–7. doi:10.1192/bjp.181.43.s50
71. Hirjak D, Wolf RC, Wilder-Smith EP, Kubera KM, Thomann PA. Motor abnormalities and basal ganglia in schizophrenia: evidence from structural magnetic resonance imaging. *Brain Topogr* (2014). doi:10.1007/s10548-014-0377-3
72. Crespi B, Badcock C. Psychosis and autism as diametrical disorders of the social brain. *Behav Brain Sci* (2008) **31**:241–261;discussion261–320. doi:10.1017/S0140525X08004214
73. Midorikawa A, Hashimoto R, Noguchi H, Saitoh O, Kunugi H, Nakamura K. Impairment of motor dexterity in schizophrenia assessed by a novel finger movement test. *Psychiatry Res* (2008) **159**:281–9. doi:10.1016/j.psychres.2007.04.004
74. Keefe RS, Fenton WS. How should DSM-V criteria for schizophrenia include cognitive impairment? *Schizophr Bull* (2007) **33**:912–20. doi:10.1093/schbul/sbm046
75. Irani F, Kalkstein S, Moberg EA, Moberg PJ. Neuropsychological performance in older patients with schizophrenia: a meta-analysis of cross-sectional and longitudinal studies. *Schizophr Bull* (2011) **37**:1318–26. doi:10.1093/schbul/sbq057
76. Mockler D, Riordan J, Sharma T. Memory and intellectual deficits do not decline with age in schizophrenia. *Schizophr Res* (1997) **26**:1–7.
77. Hijman R, Hulshoff Pol HE, Sitskoorn MM, Kahn RS. Global intellectual impairment does not accelerate with age in patients with schizophrenia: a cross-sectional analysis. *Schizophr Bull* (2003) **29**:509–17. doi:10.1093/oxfordjournals.schbul.a007023
78. Hedman AM, Van Haren NE, Van Baal GC, Brans RG, Hijman R, Kahn RS, et al. Is there change in intelligence quotient in chronically ill schizophrenia patients? A longitudinal study in twins discordant for schizophrenia. *Psychol Med* (2012) **42**:2535–41. doi:10.1017/S0033291712000694
79. Dragovic M, Waters FA, Jablensky A. Estimating premorbid intelligence in schizophrenia patients: demographically based approach. *Aust N Z J Psychiatry* (2008) **42**:814–8. doi:10.1080/00048670802277214

80. Cai L, Zhu X, Yi J, Bai M, Wang M, Wang Y, et al. Neurological soft signs and their relationship with measures of executive function in Chinese adolescents. *J Dev Behav Pediatr* (2013) **34**:197–203. doi:10.1097/DBP.0b013e3182825c41
81. Gupta S, Andreasen NC, Arndt S, Flaum M, Schultz SK, Hubbard WC, et al. Neurological soft signs in neuroleptic-naive and neuroleptic-treated schizophrenic patients and in normal comparison subjects. *Am J Psychiatry* (1995) **152**: 191–6.
82. Walther S, Horn H, Razavi N, Koschorke P, Muller TJ, Strik W. Quantitative motor activity differentiates schizophrenia subtypes. *Neuropsychobiology* (2009) **60**:80–6. doi:10.1159/000236448

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Received: 13 May 2014; paper pending published: 06 June 2014; accepted: 14 July 2014; published online: 06 August 2014.
*Citation: Hirjak D, Wolf RC, Koch SC, Mehl L, Kelbel JK, Kubera KM, Traeger T, Fuchs T and Thomann PA (2014) Neurological abnormalities in recent-onset schizophrenia and Asperger-syndrome. Front. Psychiatry **5**:91. doi: 10.3389/fpsyt.2014.00091*
This article was submitted to Schizophrenia, a section of the journal Frontiers in Psychiatry.

frontiers in PSYCHIATRY

REVIEW ARTICLE
published: 28 November 2014
doi: 10.3389/fpsyt.2014.00171

Hyperactivity and motoric activity in ADHD: characterization, assessment, and intervention

***Caterina Gawrilow*[1,2,3,4]*, *Jan Kühnhausen*[2,3], *Johanna Schmid*[1,4] *and Gertraud Stadler*[5]**

[1] *Faculty of Science, Department of Psychology, Eberhard Karls Universität Tübingen, Tübingen, Germany*
[2] *German Institute for International Educational Research (DIPF), Frankfurt, Germany*
[3] *Center for Research on Individual Development and Adaptive Education of Children at Risk (IDeA), Frankfurt, Germany*
[4] *LEAD Graduate School, Eberhard Karls Universität Tübingen, Tübingen, Germany*
[5] *Psychology Department, Columbia University, New York, NY, USA*

Edited by:
Sebastian Walther, University of Bern, Switzerland

Reviewed by:
Stephan Kupferschmid, University of Bern, Switzerland
Sarah Schiebler, University of Bern, Switzerland

****Correspondence:***
Caterina Gawrilow, Faculty of Science, Psychology Department, Eberhard Karls Universität Tübingen, Schleichstraße 4, Tübingen 72076, Germany
e-mail: caterina.gawrilow@uni-tuebingen.de

The aim of the present literature review is threefold. (1) We will review theories, models, and studies on symptomatic hyperactivity and motoric activity in attention-deficit/hyperactivity disorder (ADHD). (2) Another focus will be on assessment methods that have been proven to be effective in the detection of hyperactivity and motoric activity in children, adolescents, and adults with and without ADHD and emerging areas of research in the field of ADHD. We will compare subjective methods (i.e., rating scales) and objective methods (i.e., accelerometers). (3) Finally, physical activity intervention studies aiming at a modification of activity and overactive behavior will be summarized that seem to be promising candidates for alleviating hyperactivity symptoms in children, adolescents, and adults with ADHD.

Keywords: accelerometers, bifactor models of ADHD, ADHD, hyperactivity–impulsivity, physical activity, support vector machines

INTRODUCTION

Hyperactivity and a general increase in motoric activity with respect to amount/frequency and variability of activity/movements are main symptoms of both the combined and the hyperactive–impulsive type of attention-deficit/hyperactivity disorder (ADHD). Children with ADHD fidget with hands and feet, have difficulties remaining seated, run about, or climb excessively, and have difficulties to engage in activities quietly (1). Children with ADHD show increased physical activity (PA) both during the day and the night (2). Thus, research indicates that in one-third of children with ADHD and with an even higher prevalence in adults with ADHD sleep disorders (i.e., daytime sleepiness, insomnia, delayed sleep phase syndrome, fractured sleep, restless legs syndrome, and sleep disordered breathing) are common (3). Whereas children without ADHD usually outgrow hyperactivity around the age where they enter elementary school, hyperactivity remains present in children who receive an ADHD diagnosis. This leads to severe problems during structured school activities and interactions with parents, teachers, and peers. In adolescents and adults with ADHD, hyperactivity remains as a symptom, leading to, for instance, extreme restlessness and feelings of always being on the go or driven by a motor. Hyperactivity as one of the core symptoms of ADHD is thus leading to maladaptive cognitive and social functioning and disturbed well-being.

Counterintuitively though, children and adolescents with ADHD appear to be less likely to engage in regular vigorous PA and organized sports (4). Research only begins to investigate possible barriers that might constitute underlying reasons for this physical inactivity. One of the reasons might be that due to the ADHD symptoms of inattentiveness and impulsivity, affected children are easily distracted by or respond impulsively to alternative activities [e.g., watching TV (5)]. Another reason might be that deficits in executive functions that potentially underlie the ADHD symptomatology lead to difficulties initiating and maintaining PA (4, 6). Furthermore, it seems that children are at risk for not being physically active when they receive no ADHD treatment [i.e., medication with methylphenidate, MPH (7)].

While inattentiveness as a core symptom has been investigated in numerous studies, no clear characterization of symptomatic hyperactivity and motoric activity in children, adolescents, and adults with ADHD exists. In addition, there are no guidelines for the assessment and intervention of motoric activity in ADHD (8).

Therefore, aims of the present literature review are (1) to review studies on symptomatic hyperactivity and motoric activity in ADHD on different developmental stages. This is important because hyperactivity as a symptom and its possible differentiation from other symptoms as for instance inattentiveness might alter over the lifespan. (2) Another focus will be on subjective and objective assessment methods that have been proven to be effective in the detection of hyperactivity and motoric activity in ADHD. This is important because there is a need for adequate and efficient detection methods of hyperactivity in clinical settings. As we will explain in more detail, clinical diagnoses often rely on retrospective parental and teacher reports on hyperactive behavior shown by children and adolescents. (3) Finally, PA intervention studies aiming at a change or modification of activity and overactive behavior that seem to be promising candidates for alleviating hyperactivity symptoms in ADHD will be summarized.

DIAGNOSTIC CRITERIA OF SYMPTOMATIC HYPERACTIVITY AND MOTORIC ACTIVITY IN ADHD

Hyperactivity constitutes a core symptom of ADHD that represents one of the most common disorders in childhood and adolescence, with approximately 5.3% of school-aged individuals being affected (9). The Diagnostic and Statistical Manual of Mental Disorders (DSM-5) classifies ADHD as a neurodevelopmental disorder and lists 18 symptoms on two dimensions (see **Table 1**), namely, (1) hyperactivity–impulsivity and (2) inattention that manifest in three possible main presentations: (a) predominantly hyperactive/impulsive presentation (314.01), (b) predominantly inattentive presentation (314.00), and (c) combined presentation (314.01). A diagnosis requires at least six symptoms of hyperactivity–impulsivity and/or inattention in childhood and adolescence, and at least five symptoms in adulthood to be present in two or more settings (e.g., at home, school/work, with friends) for at least six months, and to interfere with developmental level and functioning.

CURRENT PSYCHOLOGICAL THEORIES OF HYPERACTIVITY AND MOTORIC ACTIVITY IN ADHD

Several psychological theories exist that address the question of what gives rise to symptomatic hyperactivity and motoric activity in ADHD. In our review we outline three current theoretical conceptions: (1) the State Regulation Model, (2) Multiple Pathway Theories, and (3) the Dynamic Developmental Theory of ADHD.

The State Regulation Model suggests that clinical levels of ADHD symptomatology can be traced back to a deficit in keeping optimal activation states (10, 11). Building up on the cognitive-energetic theory of Sanders (12) and Sanders and van Duren (13)

Table 1 | Hyperactivity–impulsivity and inattention symptoms according to DSM-5 (1).

Hyperactivity–Impulsivity

1. Often fidgets with or taps hands or feet or squirms in seat
2. Often leaves seat in situations when remaining seated is expected (e.g., leaves his or her place in the classroom, in the office or other workplace, or in other situations that require remaining in place)
3. Often runs about or climbs in situations where it is inappropriate. (Note: In adolescents or adults, may be limited to feeling restless.)
4. Often unable to play or engage in leisure activities quietly
5. Is often "on the go," acting as if "driven by a motor" (e.g., is unable to be or uncomfortable being still for extended time, as in restaurants, meetings; may be experienced by others as being restless or difficult to keep up with)
6. Often talks excessively
7. Often blurts out an answer before a question has been completed (e.g., completes people's sentences; cannot wait for turn in conversation)
8. Often has difficulty waiting his or her turn (e.g., while waiting in line)
9. Often interrupts or intrudes on others (e.g., butts into conversations, games, or activities; may start using other people's things without asking or receiving permission; for adolescents and adults, may intrude into or take over what others are doing)

Inattention symptoms

1. Often fails to give close attention to details or makes careless mistakes in schoolwork, at work, or during other activities (e.g., overlooks or misses details, work is inaccurate)
2. Often has difficulty sustaining attention in tasks or play activities (e.g., has difficulty remaining focused during lectures, conversations, or lengthy reading)
3. Often does not seem to listen when spoken to directly (e.g., mind seems elsewhere, even in the absence of any obvious distraction)
4. Often does not follow through on instructions and fails to finish schoolwork, chores, or duties in the workplace (e.g., starts tasks but quickly loses focus and is easily sidetracked)
5. Often has difficulty organizing tasks and activities (e.g., difficulty managing sequential tasks; difficulty keeping materials and belongings in order; messy, disorganized work; has poor time management; fails to meet deadlines)
6. Often avoids, dislikes, or is reluctant to engage in tasks that require sustained mental effort [e.g., schoolwork or homework (for older adolescents and adults, preparing reports, completing forms, reviewing lengthy papers)]
7. Often loses things necessary for tasks or activities [e.g., school materials, pencils, books, tools (wallets, keys, paperwork, eyeglasses, and mobile telephones)]
8. Is often easily distracted by extraneous stimuli (for older adolescents and adults, may include unrelated thoughts).
9. Is often forgetful in daily activities (e.g., doing chores, running errands; for older adolescents and adults, returning calls, paying bills, keeping appointments)

Behavioral examples added to symptom descriptions in DSM-5 compared to DSM-IV are given in square brackets. Symptoms 1–6 from the hyperactivity–impulsivity dimension denote symptoms classed as hyperactivity. Symptoms 7–9 from the hyperactivity–impulsivity dimension denote symptoms classed as impulsivity.

the model assumes that a given person's activation level increases in situations where the presentation rate of stimuli is high, and decreases in situations where the presentation rate of stimuli is low. To reach optimal levels of performance and counteract overactivation under high stimulus presentation rates as well as underactivation under low stimulus presentation rates, the allocation of extra effort (i.e., effortful control) is necessary. Several studies at various developmental stages have shown that individuals with ADHD show greatest performance deficits compared to individuals without ADHD not under medium event rates but under fast (14, 15) and slow (15, 16) event rates when the effortful allocation of extra effort would have been necessary for optimal performance. Correspondingly, the State Regulation Model postulates ADHD symptoms, including hyperactivity, to increase or decrease relative to a given person's respective state that requires effortful control. Thus, in the context of this theoretical model, levels of hyperactivity are not seen as stable across situations but to become increasingly present under low activation states as an attempt of self-stimulation and under high activation states as a behavioral sign of overactivation.

Multiple pathway conceptions (17–19) postulate that there are several distinct developmental influences (i.e., 'pathways') that converge onto a core symptom expression of ADHD but with remaining specificities (20). Today, the most prominent multiple pathway conceptions is the Triple-Pathway Model (19) that suggests dissociable *timing*, *inhibition*, and *delay deficits* to give rise to highly heterogeneous expressions of ADHD symptoms. With regard to timing, the model suggests that individuals with ADHD display deficits in, for example, the discrimination of durations and the adequate anticipation of time intervals. Inhibition deficits refer to impaired abilities of individuals with ADHD to inhibit responses in inappropriate situations (21) such as awaiting turn in communications. Delay deficits denote the aversion and enhanced negative emotional reactions to situations characterized by (temporal) delays [e.g., Ref. (22)] such as waiting for further instructions in the classroom. Within this theoretical framework, the symptom of hyperactivity is conceptualized as a behavioral attempt to attenuate negative subjective experiences of delay where delay cannot be circumvented (23).

The Dynamic Developmental Theory of ADHD (24) suggests a hypofunctioning mesolimbic dopamine branch to underlie altered reinforcement of novel behavior and insufficient extinction of behavior that has previously been reinforced. It is assumed that the critical time frame for a reinforcer to take effect is shorter in individuals with ADHD compared to individuals without ADHD. Accordingly, socially desirable behavior is frequently not positively reinforced, and undesirable behavior not negatively reinforced in time. The theory predicts that (gradually developing) hyperactivity stems from a combination of altered positive reinforcement and deficient extinction processes, leading to an increased and accumulating number of behavioral responses that may display in excess motoric activity.

STRUCTURAL ACCOUNTS OF HYPERACTIVITY AND MOTORIC ACTIVITY IN ADHD

Despite broad consensus about what classifies as hyperactivity in the context of ADHD and several theoretical approaches to its underlying causes, the question of how the symptom relates to impulsivity and inattention has been one of the main areas of scientific debate in this research field for the last 20 years. Respective research questions are (a) is hyperactivity essentially just an expression of one underlying ADHD condition? (b) Is hyperactivity distinguishable from, yet related to impulsivity and/or inattention? (c) Or is a combination of those two perspectives possible? These questions concern our understanding of hyperactivity, how it relates to functional impairment and, by association, what kind of treatment may work and for whom. Important statistical methods to address the ongoing debate are factor analyses, which directly concern the measurement structure underlying ADHD symptoms and thus the question of coherence and distinctness between hyperactivity, impulsivity, and inattention. Factor models that have been discussed are (a) the one-factor model, which assumes one underlying unitary symptom domain, (b) the correlated factor models, which assume distinct symptom domains that are correlated, and (c) bifactor models, which incorporate both an underlying unitary symptom domain and additional specific independent symptom domains.

A one-factor model assumes that there is a single dimension underlying hyperactivity as well as impulsivity and inattention. No structural distinction is made in this model between hyperactivity and other symptom domains. However, there has been abundance of empirical evidence from factor-analytic investigations convincingly showing that this factor model does not represent an adequate conceptualization [e.g., Ref. (25–27)].

Correlated factor models emphasize the separability of hyperactivity from inattention and/or impulsivity (28). They conceptualize separate, yet related, latent constructs with either two factors (i.e., representing hyperactivity–impulsivity and inattention) or three factors (i.e., representing hyperactivity, impulsivity, and inattention) without a common core, which give rise to the phenotypic representation of ADHD.

Factor-analytic studies until the beginning of the 21st century found strong support for correlated factor models being better statistical representations of the symptom structure than the one-factor model [e.g., Ref. (29–34)]. Direct comparisons of the correlated two-factor model separating hyperactivity–impulsivity and inattention into two separate dimensions, and three-factor models separating the dimensions of hyperactivity and impulsivity besides inattention are somewhat inconclusive: Whereas many studies found support for differentiating two latent symptom dimensions (26, 29–31, 35–37), others pointed to the superior fit of models with three latent symptom dimensions that emphasize the separability of hyperactivity and impulsivity [e.g., Ref. (33, 34, 38)]. However, the more parsimonious two-factor model is usually favored because separating hyperactivity from impulsivity tends to improve the overall model fit only slightly and the latent factors of hyperactivity and impulsivity are usually highly correlated (39). Nevertheless, the question has been brought up as to whether the relative underrepresentation of symptoms of impulsivity in DSM (i.e., three) compared to the number of symptoms of hyperactivity (i.e., six; see **Table 1**) and limited psychometric properties—which limit statistical power to confirm a specific factor of impulsivity—may also explain some of the conflicting results between the studies mentioned above (30, 37, 39). Overall,

it has been proposed that support for the validity of the correlated factor models comes from differential associations of the symptom domains with criterion variables of functional impairment (e.g., externalizing and internalizing behaviors). However, subscale sum scores for different symptom domains may not only represent domain specific symptom variation but also variation that can be traced to an underlying general symptom domain. Thus, such differential associations with measures of functional impairment could be compounded with influences from an underlying core symptom domain.

More recently than the one-factor model and correlated factor models, bifactor models have been proposed. They simultaneously account for both the common variance (i.e., coherence) between hyperactivity and the other core symptoms of ADHD with a latent general (g) ADHD factor, and the unique separable variance of hyperactivity, impulsivity, and inattention with specific domain factors (s) that are independent (i.e., orthogonal) from the general ADHD factor. Thus, to a greater extent than correlated factor models, bifactor models promote the common variance between symptom domains suggesting a unitary core construct underlying all ADHD symptoms, while endorsing additional covariation that manifests in orthogonal, specific symptom factors. During the last years, a number of studies have compared the more traditional correlated factor models with bifactor models and generally supported the superior model fit of the latter across a wide range of age groups (i.e., children, adolescents, adults), informants (i.e., self, parent, teacher, clinician ratings), methods of measurement (i.e., rating scales, interviews), and target populations [i.e., clinical and community samples (28, 39–48)]. Nevertheless, substantial inconsistency remains with regard to the question of whether a specific factor of hyperactivity can be distinguished from a specific factor of impulsivity (28, 40, 45, 47, 48). Just as discussed for the correlated factor models, the relative scarcity of impulsivity items may limit the power to detect a separate specific factor representing these symptoms separately from hyperactivity.

In sum, and although further studies and possibly the development of further items to assess impulsivity are needed to shed light on the question of separability between hyperactivity and impulsivity, a bifactor model framework seems to be a valid account of hyperactivity in the context of ADHD and its phenotypic representation for the following reasons: First, studies addressing the question of the development of ADHD across the lifespan reveal that it shows a substantial degree of stability and in many cases persists into adulthood (49), even though the specific symptom manifestation of this disorder may change with development [e.g., Ref. (50)]. This suggests a generic component, which lies at the core of the disorder and is stable over time, along with additional specific manifestations that may fluctuate (43). Due to the lack of a 'common core' in correlated factor models, which assume interrelated but conceptually independent symptom domains, they lack explanatory value for such a generic component. Second, quantitative genetic research (i.e., twin and adoption studies) suggest that there are sets of genes that exclusively influence hyperactivity and sets of genes that influence all domains of ADHD symptoms [(51, 52); for a review of quantitative genetic research on ADHD see (53)]. A bifactor model that represents a general ADHD symptom factor as well as independent specific symptom factors may be especially well suited to account for these findings. Third, the bifactor model has been suggested to be in line with current etiological models [e.g., Ref. (28, 43, 54)] such as multiple pathway conceptions (17–19), which postulate that there are several distinct developmental influences (i.e., 'pathways') that converge onto a core symptom expression, while specificities do remain (20).

SYMPTOMATIC HYPERACTIVITY AND MOTORIC ACTIVITY IN ADHD ON DIFFERENT DEVELOPMENTAL STAGES

Excessive motor activities are a first precursor of ADHD and often observed by parents during toddlerhood, even though they are hardly distinguishable from highly variable normative behaviors during this developmental period. Most frequently, impairing levels of hyperactivity are identified during the primary school years with a majority of children (approximately 60–85%) continuing to meet diagnostic criteria of ADHD throughout childhood and into adolescence and adulthood [e.g., Ref. (55)]. Notably, predominantly boys show symptomatic hyperactivity [e.g., Ref. (56)]. Sparse research addressing the trajectory of hyperactivity throughout development suggests a moderate stability (57). For instance, sleep problems operationalized as movements during the night (assessed by actigraphs) remain from childhood to adulthood (58). For many individuals, overt signs of hyperactivity decline from childhood into adulthood and may be confined with more subjective states such as mental restlessness, jitteriness, or impatience, indicating that the symptomatology undergoes substantial changes during the developmental course (1, 59, 60).

However, until to date, knowledge about the development of hyperactivity in the context of ADHD is limited and mainly based on retrospective self-reports of symptoms [e.g., Ref. (57)] which may well be affected by retrospective recall bias. To gain a more fine-grained understanding of the development of symptomatic hyperactivity and motoric activity across development, prospective longitudinal studies are needed that address symptom expressions as experienced by affected individuals themselves but also significant other people (e.g., parents, teachers, peers).

ASSESSMENT METHODS FOR THE DETECTION OF SYMPTOMATIC HYPERACTIVITY AND MOTORIC ACTIVITY IN ADHD

Physical activity can be assessed with a variety of measures, including subjective self-reports via survey questionnaires or more frequent daily or hourly recalls, and more objective measures such as wearable sensors (i.e., pedometers, accelerometers including those built into mobile phones, heart rate sensors), doubly labeled water, and direct observation.

So far, there is no single gold standard of measuring activity across populations (e.g., children, adolescents, adults) and across different assessment purposes [e.g., activity status in populations, relationship of activity with short-term and long-term health and well being, clinical and intervention research (61)]. With widely varying time periods assessed (from minutes to days, weeks up to several years, over the lifespan) and activity definitions regarding activity dimension and intensity, findings obtained with different activity measures can be difficult to compare. One important consideration in choosing activity measures is assessment purpose: It is important to clearly specify the research purpose as well as

the exact frequency, duration, and distribution of activity of interest and then choose the appropriate study design and assessment instrument. For example, studying sedentary behavior over several years to better understand the development of obesity will likely have to recur to questionnaires; whereas a study relating micro-movements of arms and legs to concurrent ADHD symptoms over a short time period would combine several sensors on arms and legs with frequent ADHD symptom assessments.

Self-report questionnaires are still the most commonly used method for measuring activity due to their cost effective application and low participant burden. Several reviews give an overview of available measures in children and adolescents (62–65) and adults (66–68). However, several other reviews also stated concerns about the validity of self-reported activity for youth and adults without clinical diagnoses as for instance ADHD (63, 67–70). Despite mostly acceptable reliability, the validity of PA questionnaires is still low to moderate. However, the reviews identified several questionnaires that showed both good reliability and acceptable validity [e.g., FPACQ, Flemish physical activity computerized questionnaire (71); PDPAR, previous day physical activity recall (72); RPAR, recess physical activity recall (73)]. To sum up, given that the validity of self-report questionnaires is limited in youth and adults without ADHD, their validity and reliability is even more questionable in children, adolescents, and adults with ADHD. This is because problems with inattention and impulsivity interfere with accurately noticing, memorizing, and reporting activity in a questionnaire, making reliable and valid self-reports even less likely.

Sensor-based activity assessment with pedometers and accelerometers has gained popularity in research (74–76) and in everyday life over the past years. As activity sensors shrink in size and have increasingly lasting batteries, they have become widely used in activity research in children, adolescents, and adults without ADHD. Wearable sensors require some buy-in from participants, as they have to be trained how to wear them – over the hip bone, usually putting them on in the morning and taking them off at night and during water-based activities – and have to give them back at the end of the study. Pedometers often do not store wear time in addition to steps and thus miss an important confounding variable for analysis; whereas accelerometers record wear time so that it can be included in analyses. Standard cut offs for valid days are at least 10 h of daily wear time (76). Among the disadvantages of pedometers are that they miss acceleration and speed of movement that should be especially interesting for understanding hyperactivity. Among their many advantages, pedometers are affordable (i.e., participants can even keep them after the study enabling continued self-monitoring), and they allow within-person comparisons. Pedometers and accelerometers are useful for measuring habitual activity in everyday life that is hard to capture in questionnaires because it evades conscious attention. Accelerometers can record more fine-grained activity information (i.e., speed, timing of movement) that may be particularly relevant for the assessment of hyperactivity. They can also detect movement of arms and legs if worn on wrist and ankle. However, there are also disadvantages of accelerometers and pedometers: Most devices miss water-based activities (i.e., swimming) and underestimate activities that do not involve movement of the part of the body where the sensor is located, as for example rowing or cycling with an accelerometer worn at the hip (77).

Smart phones have built-in accelerometers and can be used to measure activity. However, their assessment is less precise because the phone is not consistently worn in the same position (e.g., hand, pocket, bag). In the same vein, GPS assessments can be used but again are less precise about micro-movements. Heart rate sensors provide a comprehensive method of measuring physical exertion that captures many activities, not only vertical movement. Other methods for determining activity, such as doubly labeled water, multichannel devices combining accelerometers with respiration rate, electrocardiography, or electromyography and direct observation are expensive and can be burdensome for participants and are therefore more frequently used in smaller studies within the lab.

So far, there are few studies that have used sensor-based activity assessments in children and adolescents – and even fewer in those with ADHD. Thus, particularly in individuals with ADHD the cut-off points and algorithms for counting a movement as motion and classifying activity are still being developed. However, children diagnosed with ADHD differ from those without ADHD in the amount and intensity of their movements, as has been shown with different techniques of measuring movements, such as motion tracking systems using infrared motion analysis [(78); see also Ref. (79) for the Qb test], parent and teacher rating scales (80), and accelerometers (2). This knowledge has been used to identify children with ADHD with moderate accuracy measuring their activity with accelerometers over a 2-hour period (2) and with good accuracy measuring activity for 24 h (81).

In addition to comparisons of the amount and intensity of PA over a prolonged period of time, more fine-grained analyses of movements could also be informative. Modern accelerometers provide the opportunity to obtain data measured at very high resolutions (milli-G) and at very small time intervals (100th of a second). This allows not only for a measurement of the amount of activity, but also of more detailed qualitative differences in activities. These differences can already be detected with rather short measurement times. For example, it is possible to distinguish different kinds of activities by analyzing raw accelerometer data [e.g., Ref. (82, 83)]. In these studies, accelerometer data were accurately classified into different kinds of activities using Support Vector Machines [SVMs (84, 85)]. SVMs are machine learning techniques that allow for the classification of data into different categories. The great advantage of SVMs for this purpose lies in their ability to deal with highly complex and non-linear associations between accelerometer data and the corresponding categories of activity. Therefore, SVMs are perfectly suited to classify subjects as either having or not having ADHD. In recent years, this has already been done with quite some success with the use of different kinds of data, such as EEG (86, 87), inertial measurement units [IMU (88)], and MRI data (89–91).

These considerations indicate that fine-grained data from modern accelerometers, analyzed with SVMs, could be beneficial in two respects. First, they could be used to accurately identify children with ADHD with relatively little effort, in terms of both time and money. Second, those characteristics of accelerometer data that prove to be useful for distinguishing participants with and without

ADHD could be further analyzed. By doing so, new insights about the nature of ADHD and hyperactivity could be obtained. These insights would go beyond the concept that was used in previous accelerometer studies on ADHD, namely that children with ADHD merely show higher amounts and intensities of activity. Hence, they could help to refine the concepts related to ADHD and hyperactivity (e.g., fidgeting, jitteriness), making them more objectively accessible, and less susceptible to subjective ratings.

MODIFYING ADHD AND ADHD RELATED SYMPTOMS

Vigorous PA interventions in general address several areas that are problematic for children, adolescents, and adults with ADHD. For instance, short- and long-term interventions for increasing vigorous PA have led to improved mood and improved executive functioning (i.e., neuropsychological functions as for instance inhibition, shifting/task-switching, working memory), especially to improved inhibition performance in children, adolescents, and adults (92–94). Hence, enhancing vigorous PA could be an important additional treatment option for children with ADHD, ameliorating both comorbid affective disorders and deficits in executive functioning without potential negative side effects. Children diagnosed with ADHD might particularly benefit from PA interventions treating ADHD symptoms and comorbid problems due to various reasons: (a) PA might improve children's emotional and social functioning in addition to having a positive effect on their cognitive functioning (95–97), (b) PA prevents health problems such as weight gain and obesity, which are common in children with ADHD due to impulsive behavior as for instance impulsive unhealthy snacking (98), (c) PA does not interact negatively with other therapy programs (e.g., medication with MPH, cognitive behavioral therapy), and (d) PA can easily be integrated into the everyday routine of children (e.g., in schools).

However, only few observational and single-case studies have reported improved attention and reduced hyperactivity (i.e., fidgetiness) in children with ADHD following regular PA sessions (99). Only recently, research investigated potential benefits of vigorous PA in children and adolescents with ADHD and found positive effects of various types of short- and long-term PA interventions on behavioral, (neuro-)cognitive, and comorbid symptoms associated with ADHD (99, 100). For instance, Medina et al. (101) examined the impact of running on a treadmill for 30 min in boys diagnosed with ADHD and showed improved sustained attention irrespective of medication use. More specifically, children improved on response time and vigilance in a Continuous Performance Test while decreasing in impulsivity after being physically active for 30 min. Tantillo et al. (102) tested the efficacy of treadmill walking versus quiet rest on the management of behavioral features of ADHD in 8- to 12-year-old children compared to matched comparison children. Improved motoric functions after exercise were found only in boys with ADHD. However, findings should be considered preliminary, as the sample size was rather small (i.e., 18 participants). Finally, Pontifex et al. (103) found that a single 20-min bout of exercise (i.e., again treadmill running) improved inhibitory performance and neurocognitive functions (i.e., EEG measures) in children with ADHD in particular.

Regarding long-term PA, Gapin and Etnier (99) found that higher levels of PA as measured by accelerometers were associated with better executive function performance in 18 boys with ADHD. Moderate-to-vigorous PA predicted the performance on the Tower of London planning task and was positively associated with other executive function measures. In a randomized study, Verret et al. (104) tested the effects of a moderate- to high-intensity PA program on fitness, cognitive functioning, and ADHD symptoms over 10 weeks in 21 children diagnosed with ADHD. Children in the treatment group showed better information processing and parents reported fewer attention problems as well as a lower total number of problems at follow-up than at baseline compared to children in the control group. In a pilot study, Smith et al. (105) investigated a daily 26-min continuous moderate-to-vigorous PA program before school that lasted for 8 weeks and found positive effects on inattention, hyperactive, and impulsive symptoms in children with ADHD: Response inhibition improved following the program, and ratings by parents, teachers, and program staff indicated overall improvements of motor, cognitive, and behavioral functioning in two thirds of participating children. Jensen and Kenny (106) randomly assigned 19 boys with ADHD stabilized on medication to a 20-session yoga group or a control group with cooperative activities. Both groups improved in hyperactive and impulsive behavior and the global DSM evaluation of ADHD. However, yoga decreased oppositional, restless, and impulsive behavior, and those in the yoga group who engaged in more home practice showed greater improvement for attention and affective lability.

The aforementioned studies demonstrate potential positive effects of PA interventions in children with ADHD. However, all studies are clearly underpowered and replication studies are warranted. Moreover, this claim for replication studies is underscored by a recent meta-analysis investigating the effects of acute bouts of PA in children with ADHD in laboratory and field studies, which revealed inconclusive results (107). Some laboratory studies found significant improvements on cognitive tasks (i.e., tasks measuring visual attention referring to symptomatic attention problems in ADHD and executive functions referring to underlying cognitive deficits in ADHD). One laboratory study (108) found a significant improvement in response times in a visual attention task, one study showed a maintenance of accuracy (109), and three studies showed a significant reduction of error rates but no influence on response times (103, 110, 111).

The meta-analysis also revealed that with respect to school settings, no effects of PA (i.e., as implemented in so called active lessons) on dependent variables such as measures of attention could be found. However, subgroups as elementary school children (112) seem to benefit from PA interventions. This is important because in this age group ADHD diagnoses are given frequently compared to other age groups. Furthermore, specific sports and activities as for instance coordinative exercises seem to be particularly helpful (113).

Thus, direct positive effects of acute and chronic PA interventions on ADHD symptomatic behavior including hyperactivity seem to be possible. Still, there is scarce research revealing heterogeneous results. An important research question that is still unanswered is whether there is a direct route of improving ADHD symptoms (i.e., hyperactivity) via PA or an indirect route improving for example executive function deficits leading to a subsequent

improvement of ADHD symptoms. In the same vein it might also be the case that comorbid emotional deficits as for instance affective lability shown by children and adolescents with ADHD is altered via PA interventions leading to subsequent improvement of core ADHD symptoms (i.e., hyperactivity). More specifically, ADHD and affective problems are common co-morbidities in youths (114) and it might be the case that PA interventions target those affective problems and not the ADHD symptoms *per se*.

The association between vigorous PA and improved affect is well established and PA interventions have been shown to have positive effects on affect in healthy adults (115). While there is empirical evidence that children and adolescents accrue mental health benefits from PA interventions in general [e.g., Ref. (96)], until now, the specific link between physical activities and affect among children and adolescents has only been investigated in a few studies (116). A 10-year longitudinal study suggests that during adolescence, changes in leisure-time PA and negative affect are related inversely, that is, decreasing levels of PA are correlated with a rising prevalence of negative affect (117). In the same vein, a meta-analysis of studies investigating the depression-reducing effects of vigorous PA interventions on children and adolescents revealed effects in favor of the physically active group (118). Thus, vigorous PA is associated with lower levels of negative affect in children, adolescents, and adults in observational studies and randomized controlled trials.

Concretely, three studies have addressed the effects of PA on affective symptoms shown by children with ADHD so far. Jensen and Kenny (106) randomly assigned medicated boys with ADHD to a 20-session yoga condition or a control condition with cooperative leisure activities. Children in both conditions showed improvement in hyperactive and impulsive behaviors and in the global DSM evaluation of ADHD. Yoga decreased oppositional, restless, and impulsive behavior, and the children in the yoga condition who engaged in more home practicing of yoga showed greater improvement in attention and emotional stability. Kiluk et al. (119) found that participation in PA predicted less severe anxiety and depression in children with ADHD. Scores on parental reports of affect and behavior indicated that children with ADHD who participated in three or more sports displayed fewer symptoms of anxiety and depression compared to those children with ADHD who participated in fewer than three sports. Verret et al. (104) found in their exploratory but randomized study that teachers reported lower anxiety-depression scores and fewer social problems in children with ADHD after a 10-week PA program. In summary, PA interventions appear to improve not only executive functioning but also negative affect in children with and without ADHD.

SUMMARY

A bifactor model that represents a general ADHD symptom factor as well as independent specific symptom factors seems to be the best model to characterize the disorder. With regard to measuring hyperactivity as one of the ADHD symptoms only few studies have used sensor-based activity assessments in children and adolescents with ADHD. However, fine-grained accelerometer data analyzed with SVMs could potentially be useful to distinguish children with hyperactivity symptoms from those showing no hyperactivity symptoms. Moreover, further studies might also want to investigate the influence of medication (with MPH and Atomoxetine) and cognitive behavioral therapy on accelerometer data analyzed with SVMs. This is important because results could potentially inform about optimal treatments for individual children (i.e., tailored therapy). In order to gain further insight into the usefulness of PA interventions for children with motoric activity and hyperactivity as in children with diagnosed ADHD, it is important to investigate effects of PA regarding several aspects. First, the effects of everyday PA (i.e., biking to school, active lessons in school) and organized, structured sports need to be disentangled. Second, the dose–response relationship is in the need of being investigated: How often and for how long should children with ADHD take part in physical activities to receive an optimal level of their symptomatic behavior (i.e., fidgetiness in school). Third, interactions of medication with MPH or Atomoxetine and PA are understudied as well.

ACKNOWLEDGMENTS

The preparation of this paper was partly funded by the federal state government of Hesse (LOEWE initiative). We acknowledge support from Deutsche Forschungsgemeinschaft and Open Access Publishing Fund of Tuebingen University.

REFERENCES

1. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders.* 5th ed. Arlington, VA: American Psychiatric Publishing (2013).
2. Wood AC, Asherson P, Rijsdijk F, Kuntsi J. Is overactivity a core feature in ADHD? Familial and receiver operating characteristic curve analysis of mechanically assessed activity level. *J Am Acad Child Adolesc Psychiatry* (2009) **48**:1023–30. doi:10.1097/CHI.0b013e3181b54612
3. Yoon SYR, Jain U, Shapiro C. Sleep in ADHD in children and adults: past present, and future. *Sleep Med Rev* (2012) **16**:371–88. doi:10.1016/j.smrv.2011.07.001
4. Cook BG, Li D, Heintrich KM. Obesity, physical activity, and sedentary behavior of youth with learning disabilities and ADHD. *J Learn Disabil* (2014). doi:10.1177/0022219413518582
5. Anderson SE, Cohen P, Naumova EN, Must A. Association of depression and anxiety disorders with weight change in a prospective community-based study of children followed up into adulthood. *Arch Pediatr Adolesc Med* (2006) **160**(3):285. doi:10.1001/archpedi.160.3.285
6. Davis C, Levitan R, Smith M, Tweed M, Curtis C. Association among overeating, overweight, and attention deficit/hyperactivity disorder: a structural equations modeling approach. *Eat Behav* (2006) **7**:266–74. doi:10.1016/j.eatbeh.2005.09.006
7. Kim J, Mutyala B, Agiovlasitis S, Fernhall B. Health behaviors and obesity among US children with attention deficit hyperactivity disorder by gender and medication use. *Prev Med* (2011) **52**(3–4):218–22. doi:10.1016/j.ypmed.2011.01.003
8. Gawrilow C, Stadler G, Langguth N, Naumann A, Boeck A. Physical activity, affect, and cognition in children with symptoms of attention deficit hyperactivity disorder. *J Atten Disord* (2013). doi:10.1177/1087054713493318
9. Polanczyk G, de Lima MS, Horta BL, Biederman J, Rohde LA. The worldwide prevalence of ADHD: a systematic review and metaregression analysis. *Am J Psychiatry* (2007) **164**(6):942–8. doi:10.1176/appi.ajp.164.6.942
10. Van der Meere J. The role of attention. In: Sandberg S, editor. *Monographs on Child and Adolescent Psychiatry* Second Edition. Cambridge: University Press (2002). p. 162–213.
11. Van der Meere J. State regulation and attention deficit hyperactivity disorder. In: Gozal D, Molfese DL, editors. *Attention Deficit Hyperactivity Disorder: from Genes to Patients.* Totawa: Humana Press Inc (2005). p. 162–213.
12. Sanders AF. Towards a model of stress and performance. *Acta Psychol* (1983) **53**:61–97. doi:10.1016/0001-6918(83)90016-1

13. Sanders AF, van Duren LL. Stimulus control of visual fixation duration in a single saccade paradigm. *Acta Psychol* (1998) **99**:163–76. doi:10.1016/S0001-6918(98)00009-2
14. Sonuga-Barke EJS. Interval length and time-use by children with AD/HD: a comparison of four models. *Journal of Abnormal Child Psychology* (2002) **30**(3):257–64.
15. Van der Meere J, Vreeling H, Sergeant J. A motor presetting study in hyperactive, learning disabled and control children. *J Child Psychol Psychiatry* (1992) **33**(8):1347–54. doi:10.1111/j.1469-7610.1992.tb00954.x
16. Scheres A, Oosterlaan J, Sergeant JA. Response execution and inhibition in children with AD/HD and other disruptive disorders: the role of behavioural activation. *J Child Psychol Psychiatry* (2001) **42**(3):347–57. doi:10.1111/1469-7610.00728
17. Nigg JT, Goldsmith HH, Sachek J. Temperament and attention deficit hyperactivity disorder: the development of a multiple pathway model. *J Clin Child Adolesc Psychol* (2004) **33**(1):42–53. doi:10.1207/S15374424JCCP3301_5
18. Sonuga-Barke EJS. The dual pathway model of AD/HD: an elaboration of neuro-developmental characteristics. *Neurosci Biobehav Rev* (2003) **27**(7):593–604. doi:10.1016/j.neubiorev.2003.08.005
19. Sonuga-Barke EJS, Bitsakou P, Thompson M. Beyond the dual pathway model: evidence for the dissociation of timing, inhibitory, and delay-related impairments in attention-deficit/hyperactivity disorder. *J Am Acad Child Adolesc Psychiatry* (2010) **49**(4):345–55. doi:10.1097/00004583-201004000-00009
20. Chen FF, West S, Sousa K. A comparison of bifactor and second-order models of quality of life. *Multivariate Behav Res* (2006) **41**(2):189–225. doi:10.1207/s15327906mbr4102_5
21. Barkley RA. *Defiant Children: A Clinician's Manual for Assessment and Parent Training*. New York: Guilford Press (1997).
22. Wilbertz G, Trueg A, Sonuga-Barke EJ, Blechert J, Philipsen A, van Elst L. Neural and psychophysiological markers of delay aversion in attention-deficit hyperactivity disorder. *J Abnorm Psychol* (2013) **122**:566–72. doi:10.1037/a0031924
23. Sonuga-Barke EJS. On dysfunction and function in psychological accounts of childhood disorder. *J Child Psychol Psychiatry* (1994) **42**:199–210.
24. Sagvolden T, Johansen EB, Aase H, Russell VA. A dynamic developmental theory of attention-deficit/hyperactivity disorder (ADHD) predominantly hyperactive/impulsive and combined subtypes. *Behav Brain Sci* (2005) **28**(3):397–419. doi:10.1017/S0140525X05000075
25. Bauermeister J, Bird H, Canino G, Rubio-Stipec M, Bravo M, Alegría M. Dimensions of attention deficit hyperactivity disorder: findings from teacher and parent reports in a community sample. *J Clin Child Psychol* (1995) **24**(3):264–71. doi:10.1207/s15374424jccp2403_3
26. DuPaul GJ, Anastopoulos AD, Power TJ, Reid R, Ikeda MJ, McGoey KE. Parent ratings of attention-deficit/hyperactivity disorder symptoms: factor structure and normative data. *J Psychopathol Behav Assess* (1998) **20**(1):83–102. doi:10.1023/A:1023087410712
27. Lahey B, Pelham W, Schaughency EA, Atkins MS, Murphy HA, Hynd G, et al. Dimensions and types of attention deficit disorder. *J Am Acad Child Adolesc Psychiatry* (1988) **27**(3):330–5. doi:10.1097/00004583-198805000-00011
28. Gibbins C, Toplak ME, Flora DB, Weiss MD, Tannock R. Evidence for a general factor model of ADHD in adults. *J Atten Disord* (2012) **16**(8):635–44. doi:10.1177/1087054711416310
29. Bauermeister J, Alegría M, Bird HR, Rubio-Stipec M, Canino G. Are attentional-hyperactivity deficits unidimensional or multidimensional syndromes? Empirical findings from a community survey. *J Am Acad Child Adolesc Psychiatry* (1992) **31**(3):423–31. doi:10.1097/00004583-199205000-00007
30. Burns GL, Boe B, Walsh JA, Sommers-Flanagan R, Teegarden LA. A confirmatory factor analysis on the DSM-IV ADHD and ODD symptoms: what is the best model for the organization of these symptoms? *J Abnorm Child Psychol* (2001) **29**(4):339–49. doi:10.1023/A:1010314030025
31. Collett BR. The factor structure of DSM-IV attention deficit-hyperactivity symptoms: a confirmatory factor analysis of the ADHD-SRS. *J Psychoeduc Assess* (2000) **18**(4):361–73. doi:10.1177/073428290001800406
32. Glutting JJ, Youngstrom EA, Watkins MW. ADHD and college students: exploratory and confirmatory factor structures with student and parent data. *Psychol Assess* (2005) **17**(1):44–55. doi:10.1037/1040-3590.17.1.44
33. Gomez R, Harvey J, Quick C, Scharer I, Harris G. DSM-IV AD/HD: confirmatory factor models, prevalence, and gender and age differences based on parent and teacher ratings of Australian primary school children. *J Child Psychol Psychiatry* (1999) **40**(2):265–74. doi:10.1111/1469-7610.00440
34. Span SA, Earleywine M, Strybel TZ. Confirming the factor structure of attention deficit hyperactivity disorder symptoms in adult, nonclinical samples. *J Psychopathol Behav Assess* (2002) **24**(2):129–36. doi:10.1023/A:1015396926356
35. Rohde LA, Barbosa G, Polanczyk G, Eizirik M, Rasmussen ER, Neuman RJ, et al. Factor and latent class analysis of DSM-IV ADHD symptoms in a school sample of Brazilian adolescents. *J Am Acad Child Adolesc Psychiatry* (2001) **40**(6):711–8. doi:10.1097/00004583-200106000-00017
36. Molina BS, Smith BH, Pelham WE. Factor structure and criterion validity of secondary school teacher ratings of ADHD and ODD. *J Abnorm Child Psychol* (2001) **29**(1):71–82. doi:10.1023/A:1005203629968
37. Wolraich M, Lambert E. Teachers' screening for attention deficit/hyperactivity disorder: comparing multinational samples on teacher ratings of ADHD. *J Abnorm Child Psychol* (2003) **31**(4):445–55. doi:10.1023/A:1023847719796
38. Pillow DR, Pelham WE, Hoza B, Molina BS, Stultz CH. Confirmatory factor analyses examining attention deficit hyperactivity disorder symptoms and other childhood disruptive behaviors. *J Abnorm Child Psychol* (1998) **26**(4):293–309. doi:10.1023/A:1022658618368
39. Ullebø AK, Breivik K, Gillberg C, Lundervold AJ, Posserud M-B. The factor structure of ADHD in a general population of primary school children. *J Child Psychol Psychiatry* (2012) **53**(9):927–36. doi:10.1111/j.1469-7610.2012.02549.x
40. Caci HM, Morin AJ, Tran A. Teacher ratings of the ADHD-RS IV in a community sample: results from the ChiP-ARD study. *J Atten Disord* (2013). doi:10.1177/1087054712473834
41. Dumenci L, McConaughy SH, Achenbach TM. A hierarchical three-factor model of inattention-hyperactivity–impulsivity derived from the attention problems syndrome of the teacher's report form. *School Psych Rev* (2004) **33**(2):287–301.
42. Gomez R, Vance A, Gomez RM. Validity of the ADHD bifactor model in general community samples of adolescents and adults, and a clinic-referred sample of children and adolescents. *J Atten Disord* (2013). doi:10.1177/1087054713480034
43. Martel MM, von Eye A, Nigg JT. Revisiting the latent structure of ADHD: is there a "g" factor? *J Child Psychol Psychiatry* (2010) **51**(8):905–14. doi:10.1111/j.1469-7610.2010.02232.x
44. Martel MM, von Eye A, Nigg J. Developmental differences in structure of attention-deficit/hyperactivity disorder (ADHD) between childhood and adulthood. *Int J Behav Dev* (2012) **36**(4):279–92. doi:10.1177/0165025412444077
45. Morin AJS, Tran A, Caci H. Factorial validity of the ADHD adult symptom rating scale in a French community sample: results from the ChiP-ARD study. *J Atten Disord* (2013). doi:10.1177/1087054713488825
46. Normand S, Flora DB, Toplak ME, Tannock R. Evidence for a general ADHD factor from a longitudinal general school population study. *J Abnorm Child Psychol* (2012) **40**(4):555–67. doi:10.1007/s10802-011-9584-5
47. Toplak ME, Pitch A, Flora DB, Iwenofu L, Ghelani K, Jain U, et al. The unity and diversity of inattention and hyperactivity/impulsivity in ADHD: evidence for a general factor with separable dimensions. *J Abnorm Child Psychol* (2009) **37**(8):1137–50. doi:10.1007/s10802-009-9336-y
48. Toplak ME, Sorge GB, Flora DB, Chen W, Banaschewski T, Buitelaar J, et al. The hierarchical factor model of ADHD: invariant across age and national groupings? *J Child Psychol Psychiatry* (2012) **53**(3):292–303. doi:10.1111/j.1469-7610.2011.02500.x
49. Faraone SV, Biederman J, Mick E. The age-dependent decline of attention deficit hyperactivity disorder: a meta-analysis of follow-up studies. *Psychol Med* (2006) **36**(2):159–65. doi:10.1017/S003329170500471X
50. Lahey B, Pelham W, Loney J, Lee SS, Willcutt E. Instability of the DSM-IV subtypes of ADHD from preschool through elementary school. *Arch Gen Psychiatry* (2005) **62**:896–902. doi:10.1001/archpsyc.62.8.896
51. Greven CU, Asherson P, Rijsdijk FV, Plomin R. A longitudinal twin study on the association between inattentive and hyperactive-impulsive ADHD symptoms. *J Abnorm Child Psychol* (2011) **39**(5):623–32. doi:10.1007/s10802-011-9513-7
52. McLoughlin G, Ronald A, Kuntsi J, Asherson P, Plomin R. Genetic support for the dual nature of attention deficit hyperactivity disorder: substantial genetic overlap between the inattentive and hyperactive-impulsive components. *J Abnorm Child Psychol* (2007) **35**(6):999–1008. doi:10.1007/s10802-007-9149-9
53. Frazier-Wood AC, Rommel AS, Kuntsi J. Attention deficit hyperactivity disorder: insight from quantitative genetic research. In: Rhee SH, Ronald A,

editors. *Behavior Genetics of Psychopathology*, Vol. 1. New York: Springer (2014). p. 1–32. doi:10.1007/978-1-4614-9509-3_1
54. Martel M, Nikolas M, Nigg JT. Executive function in adolescents with ADHD. *J Am Acad Child Adolesc Psychiatry* (2007) **46**(11):1437–44. doi:10.1097/chi.0b013e31814cf953
55. Riddle MA, Yershova K, Lazzaretto D, Paykina N, Yenokyan G, Greenhill L, et al. the preschool attention-deficit/hyperactivity disorder treatment study (PATS) 6-year follow-up. *J Am Acad Child Adolesc Psychiatry* (2013) **52**(3):264.e–78.e. doi:10.1016/j.jaac.2012.12.007
56. Larsson H, Dilshad R, Lichtenstein P, Barker ED. Developmental trajectories of DSM-IV symptoms of attention-deficit/hyperactivity disorder: genetic effects, family risk and associated psychopathology. *J Child Psychol Psychiatry* (2011) **52**(9):954–63. doi:10.1111/j.1469-7610.2011.02379.x
57. Kessler R, Green J. Structure and diagnosis of adult attention-deficit/ hyperactivity disorder: analysis of expanded symptom criteria from the adult ADHD clinical diagnostic scale. *Arch Gen Psychiatry* (2010) **67**(11):1168–78. doi:10.1001/archgenpsychiatry.2010.146
58. Gamble KL, May RS, Besing RC, Tankersly AP, Fargasaon RE. Delayed sleep timing and symptoms in adults with ADHD: a controlled actigraphy study. *Chronobiol Int* (2013) **30**:598–606. doi:10.3109/07420528.2012.754454
59. Biederman J, Mick E, Faraone SV. Age-dependent decline of symptoms of attention deficit hyperactivity disorder: impact of remission definition and symptom type. *Am J Psychiatry* (2000) **157**(5):816–8. doi:10.1176/appi.ajp.157.5.816
60. Millstein RB, Wilens TE, Biederman J, Spencer TJ. Presenting ADHD symptoms and subtypes in clinically referred adults with ADHD. *J Atten Disord* (1997) **2**(3):159–66. doi:10.4088/JCP.08m04785pur
61. Troiano RP. Large-scale applications of accelerometers: new frontiers and new questions. *Med Sci Sports Exerc* (2007) **39**(9):1501. doi:10.1097/mss.0b013e318150d42e
62. Adamo KB, Prince SA, Tricco AC, Connor-Gorber S, Tremblay M. A comparison of indirect versus direct measures for assessing physical activity in the pediatric population: a systematic review. *Int J Pediatr Obes* (2009) **4**:2–27. doi:10.1080/17477160802315010
63. Chinapaw MJ, Mokkink LB, van Poppel MN, van Mechelen W, Terwee CB. Physical activity questionnaires for youth: a systematic review of measurement properties. *Sports Med* (2010) **40**:539–63. doi:10.2165/11530770-000000000-00000
64. Kohl HW, Fulton JE, Caspersen CJ. Assessment of physical activity among children and adolescents: a review and synthesis. *Prev Med* (2000) **31**:54–76. doi:10.1006/pmed.1999.0542
65. Oliver M, Schofield GM, Kolt GS. Physical activity in preschoolers: understanding prevalence and measurement issues. *Sports Med* (2007) **37**:1045–70. doi:10.2165/00007256-200737120-00004
66. Pereira MA, Fitzergerald SJ, Gregg EW, Joswiak ML, Ryan WJ, Suminski RR, et al. A collection of physical activity questionnaires for health-related research. *Med Sci Sports Exerc* (1997) **29**:S1–205.
67. Helmerhorst HJ, Brage S, Warren J, Besson H, Ekelund U. A systematic review of reliability and objective criterion-related validity of physical activity questionnaires. *Int J Behav Nutr Phys Act* (2012) **9**(1):1–55. doi:10.1186/1479-5868-9-103
68. Van Poppel MN, Chinapaw MJ, Mokkink LB, van Mechelen W, Terwee CB. Physical activity questionnaires for adults: a systematic review of measurement properties. *Sports Med* (2010) **40**:565–600. doi:10.2165/11531930-000000000-00000
69. Prince SA, Adamo KB, Hamel ME, Hardt J, Gorber SC, Tremblay M. A comparison of direct versus self-report measures for assessing physical activity in adults: a systematic review. *Int J Behav Nutr Phys Act* (2008) **5**:56–80. doi:10.1186/1479-5868-5-56
70. Sallis JF, Saelens BE. Assessment of physical activity by self report: status, limitations, and future directions. *Res Q Exerc Sport* (2000) **71**:1–14.
71. Matton L, Wijndaele K, Duvigneaud N, Duquet W, Philippaerts R, Thomis M, et al. Reliability and validity of the Flemish physical activity computerized questionnaire in adults. *Res Q Exerc Sport* (2007) **78**:293–306. doi:10.1080/02701367.2007.10599427
72. Allor KM, Pivarnik JM. Stability and convergent validity of three physical activity assessments. *Med Sci Sports Exerc* (2001) **33**:671–6. doi:10.1097/00005768-200104000-00025
73. Martinez-Gomez D, Calabro MA, Welk GJ, Marcos A, Veiga OL. Reliability and validity of a school recess physical activity recall in Spanish youth. *Pediatr Exerc Sci* (2010) **22**:218–30.
74. Baptista F, Santos DA, Silva AM, Mota J, Santos R, Vale S, et al. Prevalence of the portuguese population attaining sufficient physical activity. *Med Sci Sports Exerc* (2012) **44**:466–73. doi:10.1249/MSS.0b013e318230e441
75. Hansen BH, Kolle E, Dyrstad SM, Holme I, Anderssen SA. Accelerometer-determined physical activity in adults and older people. *Med Sci Sports Exerc* (2012) **44**:266–72. doi:10.1249/MSS.0b013e31822cb354
76. Troiano RP, Berrigan D, Dodd KW, Masse LC, Tilert T, McDowell M. Physical activity in the United States measured by accelerometer. *Med Sci Sports Exerc* (2008) **40**:181–8. doi:10.1249/mss.0b013e31815a51b3
77. Trost SG, McIver KL, Pate RR. Conducting accelerometer-based activity assessments in field-based research. *Med Sci Sports Exerc* (2005) **37**(11):531–43. doi:10.1249/01.mss.0000185657.86065.98
78. Teicher MH, Ito Y, Glod CA, Barber NI. Objective measurement of hyperactivity and attentional problems in ADHD. *J Am Acad Child Adolesc Psychiatry* (1996) **35**:334–42. doi:10.1097/00004583-199603000-00015
79. Ramtvedt BE, Roinas E, Aabech HS, Sundet KS. Clinical gains from including both dextroamphetamine and methylphenidate in stimulant trials. *J Child Adolesc Psychopharmacol* (2013) **23**:597–604. doi:10.1089/cap.2012.0085
80. Tseng W-L, Kawabata Y, Gau SS-F, Crick NR. Symptoms of ADHD and peer functioning: a transactional model of development. *J Abnorm Child Psychol* (2014) **42**:1353–65. doi:10.1007/s10802-014-9883-8
81. Martín-Martínez D, Casaseca-de-la-Higuera P, Alberola-López S, Andrés-de-Llano J, López-Villalobos JA, Ardura-Fernández J, et al. Nonlinear analysis of actigraphic signals for the assessment of the attention-deficit/hyperactivity disorder (ADHD). *Med Eng Phys* (2012) **34**(9):1317–29. doi:10.1016/j.medengphy.2011.12.023
82. He Z, Jin L. *Activity Recognition from Acceleration Data Based on Discrete Cosine Transform and SVM*. San Antonio, TX: Proceedings of the IEEE International Conference on systems, man, and Cybernetics – SMC 2009 (2009).
83. Kühnhausen J, Leonhardt A, Dirk J, Schmiedek F. Physical activity and affect in elementary school children's daily lives. *Front Psychol* (2013) **4**:456. doi:10.3389/fpsyg.2013.00456
84. Boser BE, Guyon IM, Vapnik VN. A training algorithm for optimal margin classifiers. In: Haussler D, editor. *Proceedings of the 5th Annual ACM Workshop on Computational Learning Theory COLT'92*. Pittsburgh, PA: ACM Press (1992). p. 144–52.
85. Cortes C, Vapnik VN. Support-vector networks. *Mach Learn* (1995) **20**:273–97. doi:10.1023/A:1022627411411
86. Abibullaev B, An J. Decision support algorithm for diagnosis of ADHD using electroencephalograms. *J Med Syst* (2012) **36**:2675–88. doi:10.1007/s10916-011-9742-x
87. Mueller A, Candrian G, Kropotov JD, Ponomarev VA, Baschera GM. Classification of ADHD patients on the basis of independent ERP components using a machine learning system. *Nonlinear Biomed Phys* (2010) **4**(Suppl 1):S1. doi:10.1186/1753-4631-4-S1-S1
88. O'Mahony N, Florentino-Liano B, Carballo JJ, Baca-García E, Rodríguez AA. Objective diagnosis of ADHD using IMUs. *Med Eng Phys* (2014) **36**:922–6. doi:10.1016/j.medengphy.2014.02.023
89. Chang CW, Ho CC, Chen JH. ADHD classification by a texture analysis of anatomical brain MRI data. *Front Syst Neurosci* (2012) **6**:66. doi:10.3389/fnsys.2012.00066
90. Colby JB, Rudie JD, Brown JA, Douglas PK, Cohen MS, Shehzad Z. Insights into multimodal imaging classification of ADHD. *Front Syst Neurosci* (2012) **6**:59. doi:10.3389/fnsys.2012.00059
91. Johnston BA, Mwangi B, Matthews K, Coghill D, Konrad K, Steele JD. Brainstem abnormalities in attention deficit hyperactivity disorder support high accuracy individual diagnostic classification. *Hum Brain Mapp* (2014) **35**:5179–89. doi:10.1002/hbm.22542
92. Barenberg J, Berse T, Dutke S. Executive functions in learning processes: do they benefit from physical activity? *Educ Res Rev* (2011) **6**:208–22. doi:10.1016/j.edurev.2011.04.002
93. Best JR. Effects of physical activity on children's executive function: contributions of experimental research on aerobic exercise. *Dev Rev* (2010) **30**:331–51. doi:10.1016/j.dr.2010.08.001

94. Colcombe S, Kramer AF. Fitness effects on the cognitive function of older adults: a meta-analytic study. *Psychol Sci* (2003) **14**:125–30. doi:10.1111/1467-9280.t01-1-01430
95. Ahn S, Feweda AL. A meta-analysis of the relationship between children's physical activity and mental health. *J Pediatr Psychol* (2011) **36**:385–97. doi:10.1093/jpepsy/jsq107
96. Biddle SJH, Asare M. Physical activity and mental health in children and adolescents: a review of reviews. *Br J Sports Med* (2011) **45**:886–95. doi:10.1136/bjsports-2011-090185
97. Dunn AL, Weintraub P. Exercise in the prevention and treatment of adolescent depression: a promising but little researched intervention. *Am J Lifestyle Med* (2008) **2**(6):1–12. doi:10.1177/1559827608323225
98. Cortese S, Angriman M, Maffeis C, Isnard P, Konofal E, Lecendreux M, et al. Attention – deficit/hyperactivity disorder (ADHD) and obesity: a systematic review of the literature. *Crit Rev Food Sci Nutr* (2008) **48**:524–37. doi:10.1080/10408390701540124
99. Gapin JI, Etnier JL. The relationship between physical activity and executive function performance in children with attention-deficit hyperactivity disorder. *J Sport Exerc Psychol* (2010) **32**:753–63.
100. Gapin JI, Labban JD, Etnier JL. The effects of physical activity on attention deficit hyperactivity disorder symptoms: the evidence. *Prev Med* (2011) **52**:S70–4. doi:10.1016/j.ypmed.2011.01.022
101. Medina JA, Netto TL, Muszkat M, Medina AC, Botter D, Orbetelli R, et al. Exercise impact on sustained attention of ADHD children, methylphenidate effects. *Atten Defic Hyperact Disord* (2010) **2**(1):49–58. doi:10.1007/s12402-009-0018-y
102. Tantillo M, Kesick CM, Hynd GW, Dishman RK. The effects of exercise on children with attention-deficit hyperactivity disorder. *Med Sci Sports Exerc* (2002) **34**(2):203–12. doi:10.1097/00005768-200202000-00004
103. Pontifex MB, Saliba BJ, Raine LB, Picchietti DL, Hillman CH. Exercise improves behavioral, neurocognitive, and scholastic performance in children with attention-deficit/hyperactivity disorder. *J Pediatr* (2013) **162**:543–51. doi:10.1016/j.jpeds.2012.08.036
104. Verret C, Guay M-C, Berthiaume C, Gardiner P, Béliveau L. A physical activity program improves behavior and cognitive functions in children with ADHD: an exploratory study. *J Atten Disord* (2012) **16**:71–80. doi:10.1177/1087054710379735
105. Smith AL, Hoza B, Linnea K, McQuade JD, Tomb M, Vaughn AJ, et al. Pilot physical activity intervention reduces severity of ADHD symptoms in young children. *J Atten Disord* (2013) **17**:70. doi:10.1177/1087054711417395
106. Jensen PS, Kenny DT. The effects of yoga on the attention and behavior of boys with attention-deficit/hyperactivity disorder (ADHD). *J Atten Disord* (2004) **7**:205–16. doi:10.1177/108705470400700403
107. Janssen M, Toussaint HM, van Mechelen W, Verhagen EA. Effects of acute bouts of physical activity on children's attention: a systematic review of the literature. *Springerplus* (2014) **3**:410. doi:10.1186/2193-1801-3-410
108. Cereatti L, Casella R, Manganelli M, Pesce C. Visual attention in adolescents: facilitating effects of sport expertise and acute physical exercise. *Psychol Sport Exerc* (2009) **10**:136–45. doi:10.1016/j.psychsport.2008.05.002
109. Drollette ES, Shishido T, Pontifex MB, Hillman CH. Maintenance of cognitive control during and after walking in preadolescent children. *Med Sci Sports Exerc* (2012) **44**(10):2017–24. doi:10.1249/MSS.0b013e318258bcd5
110. Hillman CH, Pontifex MB, Raine LB, Castelli DM, Hall EE, Kramer AF. The effect of acute treadmill walking on cognitive control and academic achievement in preadolescent children. *Neuroscience* (2009) **159**(3):1044–54. doi:10.1016/j.neuroscience.2009.01.057
111. Drollette ES, Scudder MR, Raine LB, Moore RD, Saliba BJ, Pontifex MB, et al. Acute exercise facilitates brain function and cognition in children who need it most: an ERP study of individual differences in inhibitory control capacity. *Dev Cogn Neurosci* (2014) **7**:53–64. doi:10.1016/j.dcn.2013.11.001
112. Caterino MC, Polak ED. Effects of two types of activity on the performance of second-, third-, and fourth-grade students on a test of concentration. *Percept Mot Skills* (1999) **89**(1):245–8. doi:10.2466/pms.1999.89.1.245
113. Budde H, Voelcker-Rehage C, Pietrabyk-Kendziorra S, Ribeiro P, Tidow G. Acute coordinative exercise improves attentional performance in adolescents. *Neurosci Lett* (2008) **441**(2):219–23. doi:10.1016/j.neulet.2008.06.024
114. Biederman J, Ball SW, Monuteaux MC, Mick E, Spencer TJ, McCreary M, et al. (2008). New insights into the comorbidity between ADHD and major depression in adolescent and young adult females. *J Am Acad Child Adolesc Psychiatry* **47**:426–34. doi:10.1097/CHI.0b013e31816429d3
115. Conn VS. Depressive symptom outcomes of physical activity interventions: meta-analysis findings. *Ann Behav Med* **39**:128–38. doi:10.1007/s12160-010-9172-x
116. Dunton GF, Whalen CK, Jamner LD, Henker B, Floro JN. Using ecologic momentary assessment to measure physical activity during adolescence. *Am J Prev Med* (2005) **29**:281–7. doi:10.1016/j.amepre.2005.07.020
117. Nader PR, Bradley RH, Houts RM, McRitchie SL, O'Brien M. Moderate-to-vigorous physical activity from ages 9 to 15 years. *J Am Med Assoc* (2008) **300**:295–305. doi:10.1001/jama.300.3.295
118. Larun L, Nordheim LV, Ekeland E, Hagen KB, Heian F. Exercise in prevention and treatment of anxiety and depression among children and young people. *Cochrane Database Syst Rev* (2006) **3**:CD004691. doi:10.1002/14651858.CD004691.pub2
119. Kiluk BD, Weden S, Culotta VP. Sport participation and anxiety in children with ADHD. *J Atten Disord* (2009) **12**:499–506. doi:10.1177/1087054708320400

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Received: 01 October 2014; paper pending published: 29 October 2014; accepted: 13 November 2014; published online: 28 November 2014.

*Citation: Gawrilow C, Kühnhausen J, Schmid J and Stadler G (2014) Hyperactivity and motoric activity in ADHD: characterization, assessment, and intervention. Front. Psychiatry **5**:171. doi: 10.3389/fpsyt.2014.00171*

This article was submitted to Schizophrenia, a section of the journal Frontiers in Psychiatry.

frontiers in
PSYCHIATRY

OPINION ARTICLE
published: 06 November 2014
doi: 10.3389/fpsyt.2014.00157

Decalogue of catatonia in autism spectrum disorders

Dirk M. Dhossche*

University of Mississippi Medical Center, Jackson, MS, USA
**Correspondence: dirkdhossche@gmail.com*

Edited by:
Manuel Morrens, University Antwerp, Belgium

Reviewed by:
Manuel Morrens, University Antwerp, Belgium
Didi Rhebergen, GGZ inGeest and VU University Medical Center, Netherlands

Keywords: catatonia, autism spectrum disorders, treatment, benzodiazepines, electroconvulsive therapy

> Plaisante justice, qu'une rivière borne! Vérité au-deçà des Pyrénées, erreur au-delà.
>
> *Funny justice that is marked by a river! What is truth on this side of the Pyrenees is a mistake on the other side. (Translation by DMD)*
>
> From the book "Pensées" by Blaise Pascal (1623–1662)
> French mathematician, physicist, inventor, writer, and philosopher.

This article is an unabashed drumroll for increased recognition and treatment of catatonia in autism spectrum disorders (ASD). This new diagnostic and treatment paradigm has emerged during the last decade (1, 2) and is supported by changes in catatonia classification in DSM-5 (3) purporting to boost recognition of pediatric catatonia and catatonia in ASD (4). Findings are summarized, a vignette is presented, and a Decalogue (or "10 commandments") is offered covering rules for assessment, diagnosis, treatment, and research in the field of catatonia in ASD. Unlike the biblical Decalogue handed to Moses on Mount Sinai, these rules are hardly divine, do not mark universal truths, are mainly based on clinical experience, and need to be calibrated further as knowledge increases. They do represent the best available recommendations, at least in my opinion, for future research and in order to achieve positive outcomes that are equally rewarding for the patients and their families, and for their physicians.

PREVALENCE, ASSESSMENT, AND TREATMENT OF CATATONIA IN ASD

Catatonia is a severe but treatable syndrome that warrants prompt diagnosis and treatment with benzodiazepines and electroconvulsive therapy (ECT) and that occurs in patients of all ages, including children and adolescents (5–7). The syndrome becomes critical and life threatening in its malignant form when aggravated by fever and autonomic dysfunction. Advances in catatonia research have segued into the field of autism over the last 10 years. Catatonia in ASD has been increasingly recognized at a rate of 4–17% in adolescents and adults with ASD (**Table 1**). No systematic studies have been done in preadolescent and older (>60 years old) patients. The vignette of a 10-year-old boy with catatonia and ASD that is presented below shows its occurrence in preadolescence. There are no cases in the literature, to my knowledge, describing catatonia in patients with ASD older than 60.

Symptoms that should alert the clinician for catatonia in adolescents and young adults with ASD are markedly increased psychomotor slowness, which may alternate with excessive motor activity, apparently purposeless, and not influenced by external stimuli, extreme negativism or muteness, stereotypy, peculiarities of voluntary movement, echolalia, or echopraxia. The diagnosis of catatonia in ASD is made applying known clinical signs of catatonia and using standardized catatonia rating scales to assess the scope and the severity of the symptoms. In addition, the diagnosis may be supported by a benzodiazepine (most commonly lorazepam) challenge test, which is known to result in a marked, albeit temporary, improvement.

Stressful life events, the loss of routine, experiences of loss, interpersonal conflicts, and discrepancies between the ability in the patient and parental expectations, especially in higher functioning autistic youth, may precipitate catatonia, which may present in conjunction with other major psychiatric or medical disorders (13, 14). A medical work-up and comprehensive drug screening is necessary to uncover medical or toxic conditions.

Benzodiazepines and bilateral ECT, including maintenance ECT, should be considered as safe and effective medical treatments for pediatric catatonia and catatonia in ASD based on case-reports and case-series (2, 15). Milder cases have improved with psychological–behavioral interventions (16). Benzodiazepines, most commonly lorazepam, are the first-line treatment, followed by ECT if benzodiazepines are not or insufficiently effective. The duration and intensity of ECT varies in each case. Although there are reports of a small number of cases that show the effective use of right unilateral ECT in catatonia (17), none of these patients were diagnosed with ASD. In almost all cases with ASD, bilateral ECT has been used (18) and should be considered as the preferred method until further studies or experience shows advantages when using or starting with unilateral ECT. So far concerns of cognitive impairment with bilateral ECT have not emerged. There are now a few reported cases that have continued to receive bilateral ECT for several years to maintain improvement and to prevent relapse without any indication of cognitive or neuropsychological worsening (19, 20).

DeJong et al. (18) have recently reviewed the literature on the efficacy of various treatments for catatonia in ASD. They found 22 pertinent articles describing the treatment of 28 pediatric and adult patients supporting the use of ECT, high-dose lorazepam, and behavioral therapy. They deplore the scarcity of papers and in-depth

Table 1 | Prevalence studies of catatonia in autism spectrum disorders.

Reference	*N*	Design sample population (age, range, and/or mean)	% With catatonia (age, range, and/or mean)
Wing and Shah (8)	506	Cross-sectional referred sample with autism (NA)	17 (Age range 15–50 years, mean age = 24.6)
Billstedt et al. (9)	120	Longitudinal population sample with autism (age range 17–40 years, mean age = 25.5)	12 (NA)
Ohta et al. (10)	69	Cross-sectional referred sample with autism (NA)	12 (Age range 21–40 years, mean age = 28 SD = 5.5)
Hutton et al. (11)	135	Longitudinal referred sample with autism (age range 21–57 years, mean age = 35)	4 (NA)
Ghaziuddin et al. (12)	81	Cross-sectional referred sample with autism (mean age = 14, SD = 2)	16 (NA)

NA, not available.

analyses. They conclude that controlled multi-centers studies are warranted to compare treatments and to determine the optimal treatment for catatonia in ASD.

VIGNETTE

This vignette of a 10-year-old boy diagnosed at age 4 with high-functioning ASD, type "Asperger," who developed full-blown catatonia over the course of a few months, is the synopsis of a case-report that is in press (21).

At 4 years of age, A was diagnosed with ASD due to restrictive interests, vocal and motor tics, specific phobias, attention deficits, severe aggression, obsessive–compulsive tendencies, and abnormal movements in mouth, and repetitive movements. Testing showed an IQ of 80. At the age of 10, 1 year prior to admission for catatonia, A became extremely upset about an incident on school when his best friend spit on his thermos. Over the next few days, he became increasingly and excessively fearful that people were deliberately spitting on him. He stated that the spit could find its way into his mouth and then brain where it would ruin his identity. He refused to leave his room and go to school and went into violent rages. Over the next 6 months, several interventions and medications, including SSRI's and antipsychotics, were tried to no avail. A medical work-up included blood work, comprehensive drug testing, brain imaging and lumbar puncture, autoimmune antibodies [lupus serology, pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS) serology, anti-*N*-methyl-D-aspartate (NMDA) receptor antibodies] and was completely negative.

Six months after onset of symptoms, A started to have episodes lasting several days where he would stop speaking, refusing to eat, and sitting in the same spot in the hallway. He was diagnosed with catatonia and was started on lorazepam with positive effects but the patient took the medication inconsistently. His condition worsened. A trial of high-dose-lorazepam given intramuscularly was done, with maximum dose of 24 mg (8 mg IM three times per day), with only partial response yet no sedation. Ten months after onset of symptoms, ECT was started with consent of the parents. Bilateral ECT was started three times per week. After three ECT treatments, A started to speak a few words occasionally, mostly echoing the words (and body movements) of others. After six treatments, he started to allow others to touch him and was spitting less but continued to need help in all areas of daily function. Over the next 2 weeks ECT was continued and aripiprazole was started as an antipsychotic adjunct and titrated to 20 mg/day.

A continued to make slow progress until he became fully verbal on day 31 of admission after the 12th ECT. He carried out a long conversation with his teacher. He knew that he was in the hospital, and was oriented to season but not the month or day. A stated that he was still concerned that he would die if someone spit on him. During the next week, he improved rapidly and returned to premorbid functioning. He was discharged after two more ECT treatments. Throughout the course of ECT, no side effects were noted except an occasional headache in the afternoon on the day of ECT. His memory and cognitive function seemed greatly improved over the course of admission and ECT. At 2-year follow-up, A has had no relapses of catatonia. Maintenance therapy consists of lorazepam (4 mg/day) and aripiprazole (15 mg/day). A has been able to resume school in special education classes. The parents report that he has been back to baseline since more than 1 year.

DECALOGUE OF CATATONIA IN AUTISM SPECTRUM DISORDERS

1. Catatonia is a diagnosable syndrome in ASD (2).
2. Patients with ASD are prone to develop catatonia due to concurrent medical and psychological impairments (13, 22).
3. The treatment of catatonia in ASD is very specific and consists of benzodiazepines and ECT (23).
4. Some severe forms of repetitive self-injurious behavior (SIB) are best conceptualized as catatonic stereotypy (with bodily injury) for which benzodiazepines, ECT, and maintenance ECT are indicated (24, 25).
5. Do not use antipsychotics in the active phase of catatonia before benzodiazepines or ECT is started, in order to avoid malignant catatonia and neuroleptic malignant syndrome (23).
6. A lorazepam (initial administration of 1 or 2 mg po or parentally followed by increased doses up to 20–30 mg/day depending on the level of response and side effects or sedation) or zolpidem (5 or 10 mg po) challenge test verifies the catatonia diagnosis (23).
7. High dosages of lorazepam, up to 20–30 mg daily, may be necessary for full symptom resolution (23) and, surprisingly, are well tolerated without sedation by some patients.

8. Bilateral ECT is the definitive treatment for catatonia in ASD when lorazepam does not bring about swift or sufficient relief or when fever and autonomic dysfunction arise. Concurrent and synergistic use of lorazepam and ECT is possible when using flumazenil to temporarily suspend the anticonvulsant effects of benzodiazepines during ECT (23).
9. Maintenance ECT is a safe treatment option that is sometimes crucial to avoid relapse (19, 20).
10. Catatonia provides a window into the mechanism of autism, and vice versa (26, 27).

ROSETTA STONE

Catatonia is characterized by repetitive movements, mutism, posturing, and frantic agitation. These signs are also frequent in autism yet usually do not amount to a diagnosis of catatonia unless there is a sharp and sustained increase of these symptoms lasting days or weeks. Catatonia and autism have widely different historical roots (28). Much can be learned from the study of catatonia in ASD. The Rosetta stone was a small stone tablet containing the same message written in Greek and two different Egyptian scripts. The stone was essential for deciphering Egyptian hieroglyphics. Can the group of patients who are diagnosed with both autism and catatonia be like the Rosetta stone, providing the complete sentences required for deciphering the mechanisms of autism and catatonia? Do the syndromes have a common pathophysiology? Can the successful treatment of catatonia be applied to all patients that meet criteria for autism and catatonia? Can early application of treatments for catatonia stop autistic regression? These questions beg answers sorely needed by patients and their families.

Blaise Pascal lamented in the seventeenth century over the vagaries of justice. He observed that blasphemy in one place (or time) is truth in another place (or time). The situation is not different in medicine and also seems to apply to catatonia in ASD. Detractors interpret catatonia as an aspecific and undefined epiphenomenon of another "more valid" disorder such as a medical disorder, schizophrenia, bipolar disorder, or obsessive–compulsive disorder, requiring no specific treatment. For example, in the follow-up study of Hutton et al. (11) of 135 individuals with ASD to at least the age of 21 years, five individuals had a relatively sudden onset of catatonia and obsessive–compulsive disorder. In two cases, the disorders resolved with treatment but in the other three there was only a partial recovery. None of these patients was treated with benzodiazepines or ECT. The authors ask themselves whether benzodiazepines or ECT should have been used in these cases but then demur: "*If the impression that catatonia develops as a result of obsessive-compulsive phenomena is correct, this would not seem a strong indication. It should be added that catatonia lacks a clear definition and there would be a danger of moving too readily to heroic interventions of unproven value.*" Instead, they recommend the pharmacological and psychological approaches for obsessive–compulsive disorders unassociated with autism (or catatonia). However, the vignette and similar cases support the use of ECT in cases of ASD with catatonia, also with concurrent onset or increase of obsessions and compulsions. Of course, unfounded ethical objections to pediatric ECT, legal restrictions on pediatric ECT, lack of access to ECT in general, and stigma remain salient obstacles to effective treatment of catatonia in these challenging patients (29, 30).

REFERENCES

1. Dhossche D. Catatonia in autistic disorders (brief report). *J Autism Dev Disord* (1998) **28**:329–31. doi:10.1023/A:1026064720287
2. Dhossche D, Wing L, Ohta M, Neumarker K-J, editors. *Catatonia in Autism Spectrum Disorders*. San Diego, CA, London: Elsevier Academic Press (2006).
3. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, (5th Edition) (DSM-5)*. Washington, DC: American Psychiatric Association (2013).
4. Dhossche D, Goetz M, Gadzag G, Sienaert P. New DSM-5 category unspecified catatonia is a boost for pediatric catatonia. *Neuropsychiatry* (2013) **3**(4):401–10. doi:10.2217/npy.13.42
5. Caroff S, Mann S, Francis A, Fricchione G. *Catatonia. From Psychopathology to Neurobiology*. Washington, DC: American Psychiatric Publishing, Inc (2004).
6. Dhossche D, Wilson C, Wachtel L. Catatonia in childhood and adolescence: implications for the DSM-5. *Prim psychiatry* (2010) **17**:35–9.
7. Fink M, Taylor M. *Catatonia. A Clinician's Guide to Diagnosis and Treatment*. Cambridge: Oxford University Press (2003).
8. Wing L, Shah A. Catatonia in autistic spectrum disorders. *Br J Psychiatry* (2000) **176**:357–62. doi:10.1192/bjp.176.4.357
9. Billstedt E, Gilberg C, Gilberg C. Autism after adolescence: population-based 13- to 22-year follow-up study of 120 individuals with autism diagnosed in childhood. *J Autism Dev Disord* (2005) **35**:351–60. doi:10.1007/s10803-005-3302-5
10. Ohta M, Kano Y, Nagai Y. Catatonia in individuals with autism spectrum disorders in adolescence and early adulthood: a long-term prospective study. *Int Rev Neurobiol* (2006) **72**:41–54. doi:10.1016/S0074-7742(05)72003-1
11. Hutton J, Goode S, Murphy M, Le Couteur A, Rutter M. New-onset psychiatric disorders in individuals with autism. *Autism* (2008) **12**:373–90. doi:10.1177/1362361308091650
12. Ghaziuddin N, Dhossche D, Marcotte K. Retrospective chart review of catatonia in child and adolescent psychiatric patients. *Acta Psychiatr Scand* (2012) **125**(1):33–8. doi:10.1111/j.1600-0447.2011.01778.x
13. Dhossche D. Catatonia: the ultimate yet treatable motor reaction to fear in autism. *Autism* (2011) **1**:1. doi:10.4172/auo.1000103
14. Dhossche DM, Ross CA, Stoppelbein L. The role of deprivation, abuse, and trauma in pediatric catatonia without a clear medical cause. *Acta Psychiatr Scand* (2012) **125**(1):25–32. doi:10.1111/j.1600-0447.2011.01779.x
15. de Winter C, van Dijk F, Verhoeven W, Dhossche D, Stolker J. Autism and catatonia: successful treatment using lorazepam. A case study. *Tijdschr Psychiatr* (2007) **49**:257–61.
16. Shah A, Wing L. Psychological approaches to chronic catatonia-like deterioration in autism spectrum disorders. *Int Rev Neurobiol* (2006) **72**:245–64. doi:10.1016/S0074-7742(05)72015-8
17. Cristancho P, Jewkes D, Mon T, Conway C. Successful use of right unilateral ECT for catatonia: a case series. *J ECT* (2014) **30**(1):69–72. doi:10.1097/YCT.0b013e31829a01d3
18. DeJong H, Bunton P, Hare DJA. Systematic review of interventions used to treat catatonic symptoms in people with autistic spectrum disorders. *J Autism Dev Disord* (2014) **44**(9):2127–36. doi:10.1007/s10803-014-2085-y
19. Wachtel LE, Hermida A, Dhossche DM. Maintenance electroconvulsive therapy in autistic catatonia: a case series review. *Prog Neuropsychopharmacol Biol Psychiatry* (2010) **34**(4):581–7. doi:10.1016/j.pnpbp.2010.03.012
20. Wachtel LE, Reti IM, Dhossche DM, Slomine BS, Sanz J. Stability of neuropsychological testing during two years of maintenance electroconvulsive therapy in an autistic man. *Prog Neuropsychopharmacol Biol Psychiatry* (2011) **35**(1):301–2. doi:10.1016/j.pnpbp.2010.11.013
21. Dhossche D, van der Steen L, Shettar S. Catatonia in autism spectrum disorders: review and case-report. *Tijdschr Psychiatr* (in press).
22. Dhossche D. Autonomic dysfunction in catatonia in autism: implications of a vagal theory. *Autism* (2012) **2**(4):e114. doi:10.4172/2165-7890.1000e114
23. Dhossche D, Wachtel L. ECT for catatonia in autism. In: Ghaziuddin M, Walter G, editors. *Electroconvulsive Therapy in Children and Adolescents*. New York, NY: Oxford University Press (2013). p. 217–46.

24. Wachtel LE, Contrucci-Kuhn SA, Griffin M, Thompson A, Dhossche DM, Reti IM. ECT for self-injury in an autistic boy. *Eur Child Adolesc Psychiatry* (2009) **18**(7):458–63. doi:10.1007/s00787-009-0754-8
25. Wachtel LE, Dhossche DM. Self-injury in autism as an alternate sign of catatonia: implications for electroconvulsive therapy. *Med Hypotheses* (2010) **75**(1):111–4. doi:10.1016/j.mehy.2010.02.001
26. Dhossche D. Autism as early expression of catatonia. *Med Sci Monit* (2004) **10**:RA31–9.
27. Dhossche D, Stanfill S. Could ECT be effective in autism? *Med Hypotheses* (2004) **63**:371–6. doi:10.1016/j.mehy.2004.03.023
28. Dhossche D, Reti I, Wachtel L. Catatonia and Autism: a historical review, with implications for ECT. *J ECT* (2009) **25**:19–22. doi:10.1097/YCT.0b013e3181957363
29. Wachtel LE, Dhossche DM. Challenges of electroconvulsive therapy for catatonia in youth with intellectual disabilities: another tomato effect? *J ECT* (2012) **28**(3):151–3. doi:10.1097/YCT.0b013e31825692e2
30. Wachtel LE, Dhossche DM, Fink M, Jaffe R, Kellner CH, Weeks H, et al. ECT for developmental disability and severe mental illness. *Am J Psychiatry* (2013) **170**(12):1498–9. doi:10.1176/appi.ajp.2013.13070983

Conflict of Interest Statement: The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Received: 21 September 2014; paper pending published: 04 October 2014; accepted: 23 October 2014; published online: 06 November 2014.
Citation: Dhossche DM (2014) Decalogue of catatonia in autism spectrum disorders. Front. Psychiatry ***5****:157. doi: 10.3389/fpsyt.2014.00157*
This article was submitted to Schizophrenia, a section of the journal Frontiers in Psychiatry.

frontiers in PSYCHIATRY

ORIGINAL RESEARCH ARTICLE
published: 05 January 2015
doi: 10.3389/fpsyt.2014.00191

Physical activity in schizophrenia is higher in the first episode than in subsequent ones

Sebastian Walther*, Katharina Stegmayer, Helge Horn, Nadja Razavi, Thomas J. Müller and Werner Strik

University Hospital of Psychiatry, Bern, Switzerland

Edited by:
Mihaly Hajos, Yale University School of Medicine, USA

Reviewed by:
Manuel Morrens, University of Antwerp, Belgium
Fabian U. Lang, Ulm University, Germany

****Correspondence:***
Sebastian Walther, University Hospital of Psychiatry, Bolligenstrasse 111, Bern 60 3000, Switzerland
e-mail: walther@puk.unibe.ch

Schizophrenia is frequently associated with abnormal motor behavior, particularly hypokinesia. The course of the illness tends to deteriorate in the first years. We aimed to assess gross motor activity in patients with a first episode ($n = 33$) and multiple episodes ($n = 115$) of schizophrenia spectrum disorders using wrist actigraphy. First episode patients were younger, had higher motor activity and reduced negative symptom severity. Covarying for age, chlorpromazine equivalents, and negative symptoms, first episode patients still had higher motor activity. This was also true after excluding patients with schizophreniform disorder from the analyses. In first episode patients, but not in patients with multiple episodes, motor activity was correlated with antipsychotic dosage. In conclusion, after controlling for variables related to disorder chronicity, patients with first episodes were still more active than patients with multiple episodes. Thus, reduced motor activity is a marker of deterioration in the course of schizophrenia spectrum disorders.

Keywords: actigraphy, antipsychotic, negative symptoms, hypokinesia, psychosis

INTRODUCTION

The first episode is of particular interest to schizophrenia research because it allows assessing the clinical presentation in the absence of factors related to illness chronicity. Longitudinal studies have demonstrated a strong decline in function and quality of life during the first 2–5 years. Despite vast heterogeneity in illness course, the condition during initial episode has some predictive value (1).

Motor abnormalities are intrinsic to schizophrenia and have been reported throughout the whole course of the disorder irrespective of medication status (2–6). Particularly, psychomotor slowing impacts cognitive performance and outcome (7). Objective measures acquired with actigraphy have established hypokinesia in schizophrenia, which is correlated with negative symptom severity (8–10). However, objectively assessed gross motor activity has not been tested in first episode patients. Even though 67% of unmedicated first episode patients present with at least one motor sign (11), first episode patients tend to present with less or comparably severe negative symptoms as patients with multiple episodes (12, 13). Thus, the current study aimed to test whether physical activity as measured by wrist actigraphy would differ between first episode and multiple episode patients with schizophrenia spectrum disorders. Furthermore, we aimed to explore the association of physical activity with antipsychotic dosage and negative syndrome severity in both groups. We hypothesized that physical activity was higher in first episode patients compared to multiple episode patients, as functional decline often occurs within the early course of the disorder (1).

MATERIALS AND METHODS

PATIENTS

To explore differences between patients with a first vs. multiple episodes on physical activity, we pooled data from previous and ongoing studies applying actigraphy in schizophrenia spectrum disorders (9, 14–19). A total of 148 patients with schizophrenia spectrum disorders were included (first episode $n = 33$, multiple episodes $n = 115$). The patients with multiple episodes had on average 7.9 episodes (SD = 6.2). Diagnoses were given according to DSM-IV criteria after thorough clinical examination and review of all case files by board certified psychiatrists. The local mental health care system ensures that most of the patients are admitted to our clinic in every psychotic episode requiring inpatient treatment, allowing the collection of reliable diagnostic information. In a proportion of studies that contributed data to this analysis, the diagnoses were ascertained by structured clinical interviews such as SCID and MINI (27% of cases). Diagnoses given included paranoid schizophrenia (33% of first episode vs. 55% of multiple episode patients), catatonic schizophrenia (12 vs. 11%), disorganized schizophrenia (0 vs. 16%), schizoaffective disorder (6 vs. 5%), and schizophreniform disorder (49 vs. 13%) with significant differences between groups ($\chi^2 = 21.7$, df = 1, $p < 0.001$). Patients were excluded in case of substance abuse other than nicotine, medical conditions affecting physical activity, and epilepsy. Physical activity was recorded approximately 2 weeks after admission to the psychiatric department. At the same time, psychopathology was assessed using the positive and negative syndrome scale (PANSS) (20). Most patients were medicated (71% received atypical antipsychotics, 18% received mixed medication of typical and atypical antipsychotics, 6% received only typical antipsychotics, and 5% were medication-free at the time of our assessments). Chlorpromazine equivalents (CPZ) of the current antipsychotic pharmacotherapy were calculated according to Woods (21). In addition, diazepam equivalents (DE) were calculated according to Ashton (22). The protocols of the studies applying wrist actigraphy in schizophrenia spectrum disorders had been approved by the local ethics committee and participants provided written informed consent prior to study inclusion.

ACTIGRAPHY

Participants wore an actigraph (Actiwatch, Cambridge Neurotechnology, Inc., Cambridge, UK) for 24 consecutive hours at the wrist of the non-dominant arm. The piezoelectric sensor converts acceleration into movement counts. Data were sampled in 2 s intervals. Participants provided sleep log information and information on recording pauses (due to showering or bathing). Only the data collected during wakeful periods of the 24 h recording time were analyzed. Activity counts were averaged to provide the activity level (AL) in counts/h.

STATISTICAL ANALYSES

Demographic and clinical parameters were compared between groups by one-way ANOVAs and χ^2-tests. Since groups differed in the PANSS negative syndrome subscale score, age, and CPZ dosage, these variables were entered as covariates in an ANCOVA of AL. Furthermore, as the group of first episode patients included a large proportion of patients with schizophreniform disorder, we recalculated the ANCOVA excluding all patients with schizophreniform disorder. In order to test the additional effects of illness duration and benzodiazepine administration, we recalculated the ANCOVA first including duration of illness, negative symptoms, and CPZ as covariate and second including duration of illness, negative symptoms, CPZ, and DE as covariates. Furthermore, we compared AL in patients with different medication types (typical antipsychotics, atypical antipsychotics, and mixed medication). Next, clinical and demographic variables were correlated with AL for both groups separately. Because of the divergent results, we also calculated the interaction of CPZ and group on AL using an ANCOVA in the whole sample. Besides the classical PANSS subscores, we also tested the five PANSS factors according to van der Gaag and colleagues (23) (positive, negative, disorganization, excitement, and emotional distress), and the avolition score (sum of items N2 + N4) according to Bervoets et al. (24). All tests were performed with SPSS 21.

RESULTS

Gender distribution was not different between groups (first episode patients 61% male, multiple episode patients 57% male, $\chi^2 = 0.175$, df = 1, $p = 0.696$).

First episode patients had increased AL, were younger, received lower doses of antipsychotics and had a trend to reduced PANSS negative scores (see **Table 1**). Furthermore, first episode patients had reduced scores in the PANSS factors negative, disorganization, and excitement (23), as well as the PANSS avolition score (24).

The difference in AL between groups remained when adding the PANSS negative syndrome subscale score, age, and CPZ as covariates ($F = 6.2$, df = 4, $p < 0.001$, η^2=0.15). Furthermore, including duration of illness, negative symptoms, and CPZ as covariate did not substantially alter the results ($F = 4.53$; df = 4; $p = 0.002$; $\eta = 0.12$). Moreover, differences in AL between groups remained stable with the inclusion of duration of illness, negative symptoms, CPZ, and DE as covariates ($F = 4.23$; df = 5; $p = 0.001$; $\eta = 0.13$). Likewise, the difference in AL between groups remained when all subjects with schizophreniform disorder were excluded from the ANCOVA ($F = 4.2$, df = 4, $p = 0.003$, $\eta^2 = 0.13$) with the PANSS negative syndrome subscale score, age, and CPZ as covariates.

Table 1 | Clinical and demographic characteristics.

	First episode patients ($n = 33$)	Multiple episode patients ($n = 115$)	*F*-value	*p*-Value
Activity level (counts/h)	18057 (9194)	13551 (7047)	9.7	0.002
Age (years)	31.9 (12.5)	39.6 (11.2)	15.4	<0.001
Duration of illness (years)	1.7 (3.2)	12.7 (10.2)	30.9	<0.001
CPZ (mg)	360.2 (341.2)	530.5 (399.9)	3.9	0.049
DE (mg)	6.3 (10.5)	5.0 (10.1)	0.6	0.547
PANSS positive subscale	13.4 (4.6)	15.7 (5.6)	1.5	0.226
PANSS negative subscale	15.9 (6.5)	18.1 (6.2)	3.2	0.078
PANSS total score	61.1 (15.8)	68.7 (16.2)	5.5	0.020
PANSS avolition	4.0 (2.2)	5.0 (2.2)	5.3	0.022
PANSS factor positive	16.1 (7.1)	17.7 (6.6)	1.4	0.239
PANSS factor negative	15.2 (7.8)	18.3 (7.0)	4.6	0.033
PANSS factor disorganization	20.9 (5.7)	24.2 (6.6)	6.6	0.011
PANSS factor excitement	13.2 (3.9)	15.4 (5.3)	5.1	0.026
PANSS factor emotional distress	14.7 (6.1)	16.0 (5.5)	1.4	0.242

Numbers are given as mean (SD).

Finally, AL did not differ between groups with distinct antipsychotic medication (typical, atypical antipsychotics, and mixed medication) ($F = 0.96$; df = 2; $p = 0.386$; $\eta = 0.01$).

Correlations between AL and clinical parameters are given in **Table 2**. Associations with measures of the negative syndrome were more dominant in the patients with multiple episodes. Groups differed in the correlation of CPZ and AL, with significant effects in first episode patients and no effects in patients with multiple episodes (ANCOVA of AL with intercept between CPZ and group $F = 11.3$, df = 1, $p < 0.001$, $\eta^2 = 0.07$).

DISCUSSION

In the present study, we were able to demonstrate that patients in a first episode of schizophrenia spectrum disorders have higher physical activity than patients with multiple episodes. This result held true after controlling for negative symptoms, age, dosage of antipsychotics, and administration of benzodiazepines. Furthermore, it was still evident after excluding patients with schizophreniform disorder. Thus, we are confident that there is a true difference in physical activity between the groups beyond other major differences that are related to illness duration. Of course, the magnitude of the effect was small to medium in size as there are also other factors contributing to physical activity besides age, chronicity, and negative symptoms, such as lifestyle habits and physical constitution. Still, the mean AL value of the first episode

Table 2 | Correlation between activity level and clinical parameters.

	First episode patients		Multiple episode patients	
	r	*p*	*r*	*p*
Age	−0.21	0.251	−0.19	0.038
CPZ	−0.46	0.008	0.08	0.411
DE	−0.03	0.893	−0.29	0.002
PANSS positive syndrome score	0.07	0.698	0.13	0.163
PANSS negative syndrome score	−0.02	0.910	−0.29	0.001
PANSS total score	−0.07	0.708	−0.17	0.070
PANSS avolition factor	−0.38	0.031	−0.29	0.002
PANSS positive factor	−0.05	0.784	−0.01	0.897
PANSS negative factor	−0.33	0.064	−0.32	<0.001
PANSS disorganization factor	0.32	0.073	−0.08	0.399
PANSS excitement factor	−0.04	0.835	−0.08	0.418
PANSS emotional distress factor	−0.05	0.800	−0.13	0.183

patients is close to the mean of AL reported in different samples of healthy controls, e.g., 18000–21000 counts/h (8, 15, 25). Furthermore, subjects at ultra high risk for psychosis were shown to have reduced ALs at trend level compared to matched controls (26). Thus, even though the AL of first episode patients might still be slightly reduced compared to age matched controls, AL appear comparable to those of healthy control groups with wider age ranges. Our finding is in line with the observation that motor abnormalities are present from the first episode of schizophrenia spectrum disorders but tend to deteriorate with the progression of the disorder (2, 5). Likewise, neurocognitive measures of fine motor performance have indicated impairments in first episode patients and even more in chronic patients (27). However, it remains unknown, which factors drive the reduction of physical activity in patients with multiple episodes. Clearly, negative symptoms are related to reduced physical activity (8–10). In addition, the use of catatonia rating scales such as the modified Rogers scale (28) indicated that the frequency of the item "marked underactivity" was increased in a mixed sample of schizophrenia spectrum disorder patients as compared to first episode patients (28 vs. 9%) (11, 29). In general, motor abnormalities are prevalent in the early course but increase in frequency with multiple episodes. In many instances, it is hard to disentangle the multiple causes of hypokinesia, such as catatonia, parkinsonism, or reduced volition, i.e., negative symptoms (2). If reduction of physical activity was an indicator of deterioration, it would well fit in the observation of clinical deterioration within the first 2–5 years after the onset of schizophrenia spectrum disorders (1). First evidence suggests that hypokinesia due to parkinsonism in first episode patients was predictive of poor cognitive function after 6 months (30). However, schizophrenia presents with a heterogeneous longitudinal course and deterioration of symptoms is not everyone's fate (31).

Another important finding of the present study is the interaction of antipsychotic dosage and group on AL. Whereas, in multiple episode patients, we were unable to find a correlation of AL and CPZ, increased antipsychotic dosage was related to lower AL in first episode patients. Here, we may speculate that in first episode patients in the absence of marked negative symptoms, parkinsonism, or catatonia, antipsychotic agents may exert more impact on the overall motor activity. However, this view is partly challenged by the fact that antipsychotic agents ameliorate most psychomotor impairments in previously naïve first episode patients, including hypokinesia, parkinsonism, and catatonia (11). Still, the various antipsychotic agents currently used may exert differential effects on physical activity or spontaneous, i.e., preexisting motor symptoms. So far, only few reports exist investigating the effect of different antipsychotic agents on motor behavior in previously unmedicated subjects (32). However, we found no differences of AL in patients with different medication types (typical, atypical antipsychotics, and mixed medication).

In line with previous reports, reduced motor activity was associated with negative symptoms in both first episode and chronic schizophrenia spectrum disorders (8, 9). Also, reduced tongue movements were demonstrated to correlate with negative symptoms in first episode patients (33). Likewise, hypokinesia was associated with negative symptoms in first episode patients (11). In chronic schizophrenia, various measures of hypokinesia have demonstrated correlations with negative symptom severity, particularly the initiation of movements seems affected (2, 24, 29, 34, 35). As in one previous report, the avolition component of the negative syndrome displayed strongest correlations with spontaneous motor activity (8). Thus, our data support the assumption that actigraphy may particularly well suited to assess motivational aspects of the negative syndrome. Finally, exercise interventions have regained interest in schizophrenia targeting various problems of these patients, such as metabolic, cognitive, and social problems (36). First controlled studies reported positive effects of exercise interventions on negative symptoms and working memory in schizophrenia (37).

This study has some limitations requiring discussion. We have used data from a database to answer the research question. The methods of actigraphy and PANSS assessment were the common ground. If we had to conduct a new study on this topic, we would include more standardized measures of motor function focusing on parkinsonism and catatonia. Parkinsonism and catatonia may have influenced AL (2, 38). However, both symptoms are frequently present in patients with a first psychotic episode and in patients with multiple episodes (11). Still, these symptoms might be more frequent in patients with a chronic course of the disease (14). However, treatment with antipsychotics shows a heterogeneous effect on parkinsonism and catatonia in previously antipsychotic naïve patients: in some patients, these symptoms are ameliorated by treatment, in others they tend to emerge or deteriorate during pharmacotherapy, while in a third group symptoms remain unchanged with antipsychotic medication (32). In addition, there are better scales to assess negative symptoms (39). Still, the PANSS is a commonly used instrument, which aids data interpretation. Finally, we did not measure depressive symptoms, even though, depression might affect ALs. Patients with major depression move less than healthy controls (40). Still, in a previous investigation, we found only weak associations in major depressed patients between depression severity as assessed by the Hamilton depression rating scale (HAMD) and AL (41). However,

taking the emotional dysregulation factor according to van der Gaag (23) as a substitute parameter for depression, we failed to identify correlations with AL in any of the two groups.

In conclusion, we demonstrated that first episode patients have higher physical activity than patients with multiple episodes. The finding underlines that functional deterioration including reduced motor activity frequently occurs beyond the first episode. Thus, future studies should evaluate whether this reduction may be targeted by pharmacotherapy or specialized programs to promote physical exercise in schizophrenia (36, 42).

AUTHOR CONTRIBUTIONS

Dr. Sebastian Walther and Dr. Helge Horn designed the study. Dr. Sebastian Walther wrote the protocol. Drs. Nadja Razavi, Katharina Stegmayer, and Sebastian Walther recruited participants and performed assessments. Dr. Sebastian Walther performed the data analyses. All authors interpreted and discussed the findings. Dr. Sebastian Walther wrote the first draft of the manuscript. All authors contributed to the final version of the manuscript.

ACKNOWLEDGMENTS

Parts of this study received funding from the Bangerter-Rhyner Foundation (to Dr. Sebastian Walther) and the Swiss National Science Foundation (SNF grant 152619/1 to Dr. Sebastian Walther).

REFERENCES

1. McGlashan TH. Duration of untreated psychosis in first-episode schizophrenia: marker or determinant of course? *Biol Psychiatry* (1999) **46**(7):899–907. doi:10.1016/S0006-3223(99)00084-0
2. Walther S, Strik W. Motor symptoms and schizophrenia. *Neuropsychobiology* (2012) **66**(2):77–92. doi:10.1159/000339456
3. Wolff AL, O'Driscoll GA. Motor deficits and schizophrenia: the evidence from neuroleptic-naive patients and populations at risk. *J Psychiatry Neurosci* (1999) **24**(4):304–14.
4. Pappa S, Dazzan P. Spontaneous movement disorders in antipsychotic-naive patients with first-episode psychoses: a systematic review. *Psychol Med* (2009) **39**(7):1065–76. doi:10.1017/S0033291708004716
5. Whitty PF, Owoeye O, Waddington JL. Neurological signs and involuntary movements in schizophrenia: intrinsic to and informative on systems pathobiology. *Schizophr Bull* (2009) **35**(2):415–24. doi:10.1093/schbul/sbn126
6. Koning JP, Tenback DE, van Os J, Aleman A, Kahn RS, van Harten PN. Dyskinesia and parkinsonism in antipsychotic-naive patients with schizophrenia, first-degree relatives and healthy controls: a meta-analysis. *Schizophr Bull* (2010) **36**(4):723–31. doi:10.1093/schbul/sbn146
7. Morrens M, Hulstijn W, Sabbe B. Psychomotor slowing in schizophrenia. *Schizophr Bull* (2007) **33**(4):1038–53. doi:10.1093/schbul/sbl051
8. Docx L, Sabbe B, Provinciael P, Merckx N, Morrens M. Quantitative psychomotor dysfunction in schizophrenia: a loss of drive, impaired movement execution or both? *Neuropsychobiology* (2013) **68**(4):221–7. doi:10.1159/000355293
9. Walther S, Koschorke P, Horn H, Strik W. Objectively measured motor activity in schizophrenia challenges the validity of expert ratings. *Psychiatry Res* (2009) **169**(3):187–90. doi:10.1016/j.psychres.2008.06.020
10. Wichniak A, Skowerska A, Chojnacka-Wojtowicz J, Taflinski T, Wierzbicka A, Jernajczyk W, et al. Actigraphic monitoring of activity and rest in schizophrenic patients treated with olanzapine or risperidone. *J Psychiatr Res* (2011) **45**(10):1381–6. doi:10.1016/j.jpsychires.2011.05.009
11. Peralta V, Campos MS, De Jalon EG, Cuesta MJ. Motor behavior abnormalities in drug-naive patients with schizophrenia spectrum disorders. *Mov Disord* (2010) **25**(8):1068–76. doi:10.1002/mds.23050
12. Zhang XY, Chen da C, Xiu MH, Yang FD, Haile CN, Kosten TA, et al. Gender differences in never-medicated first-episode schizophrenia and medicated chronic schizophrenia patients. *J Clin Psychiatry* (2012) **73**(7):1025–33. doi:10.4088/JCP.11m07422
13. Vohs JL, Lysaker PH, Francis MM, Hamm J, Buck KD, Olesek K, et al. Metacognition, social cognition, and symptoms in patients with first episode and prolonged psychoses. *Schizophr Res* (2014) **153**(1–3):54–9. doi:10.1016/j.schres.2014.01.012
14. Bracht T, Heidemeyer K, Koschorke P, Horn H, Razavi N, Wopfner A, et al. Comparison of objectively measured motor behavior with ratings of the motor behavior domain of the Bern psychopathology scale (BPS) in schizophrenia. *Psychiatry Res* (2012) **198**(2):224–9. doi:10.1016/j.psychres.2011.12.038
15. Walther S, Federspiel A, Horn H, Razavi N, Wiest R, Dierks T, et al. Alterations of white matter integrity related to motor activity in schizophrenia. *Neurobiol Dis* (2011) **42**(3):276–83. doi:10.1016/j.nbd.2011.01.017
16. Walther S, Horn H, Razavi N, Koschorke P, Muller TJ, Strik W. Quantitative motor activity differentiates schizophrenia subtypes. *Neuropsychobiology* (2009) **60**(2):80–6. doi:10.1159/000236448
17. Walther S, Horn H, Razavi N, Koschorke P, Wopfner A, Muller TJ, et al. Higher motor activity in schizophrenia patients treated with olanzapine versus risperidone. *J Clin Psychopharmacol* (2010) **30**(2):181–4. doi:10.1097/JCP.0b013e3181d2ef6f
18. Walther S, Ramseyer F, Horn H, Strik W, Tschacher W. Less structured movement patterns predict severity of positive syndrome, excitement, and disorganization. *Schizophr Bull* (2014) **40**(3):585–91. doi:10.1093/schbul/sbt038
19. Walther S, Vanbellingen T, Muri R, Strik W, Bohlhalter S. Impaired pantomime in schizophrenia: association with frontal lobe function. *Cortex* (2013) **49**(2):520–7. doi:10.1016/j.cortex.2011.12.008
20. Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophr Bull* (1987) **13**(2):261–76. doi:10.1093/schbul/13.2.261
21. Woods SW. Chlorpromazine equivalent doses for the newer atypical antipsychotics. *J Clin Psychiatry* (2003) **64**(6):663–7. doi:10.4088/JCP.v64n0607
22. Ashton H. Toxicity and adverse consequences of benzodiazepine use. *Psychiatr Ann* (1995) **25**(3):158–65. doi:10.3928/0048-5713-19950301-09
23. van der Gaag M, Hoffman T, Remijsen M, Hijman R, de Haan L, van Meijel B, et al. The five-factor model of the positive and negative syndrome scale II: a ten-fold cross-validation of a revised model. *Schizophr Res* (2006) **85**(1–3):280–7. doi:10.1016/j.schres.2006.03.021
24. Bervoets C, Docx L, Sabbe B, Vermeylen S, Van Den Bossche MJ, Morsel A, et al. The nature of the relationship of psychomotor slowing with negative symptomatology in schizophrenia. *Cogn Neuropsychiatry* (2014) **19**(1):36–46. doi:10.1080/13546805.2013.779578
25. Walther S, Hugli S, Hofle O, Federspiel A, Horn H, Bracht T, et al. Frontal white matter integrity is related to psychomotor retardation in major depression. *Neurobiol Dis* (2012) **47**(1):13–9. doi:10.1016/j.nbd.2012.03.019
26. Mittal VA, Gupta T, Orr JM, Pelletier-Baldelli A, Dean DJ, Lunsford-Avery JR, et al. Physical activity level and medial temporal health in youth at ultra high-risk for psychosis. *J Abnorm Psychol* (2013) **122**(4):1101–10. doi:10.1037/a0034085
27. Mesholam-Gately RI, Giuliano AJ, Goff KP, Faraone SV, Seidman LJ. Neurocognition in first-episode schizophrenia: a meta-analytic review. *Neuropsychology* (2009) **23**(3):315–36. doi:10.1037/a0014708
28. Lund CE, Mortimer AM, Rogers D, McKenna PJ. Motor, volitional and behavioural disorders in schizophrenia. 1: assessment using the modified Rogers scale. *Br J Psychiatry* (1991) **158**(323–7):33–6. doi:10.1192/bjp.158.3.323
29. Peralta V, Cuesta MJ. Motor features in psychotic disorders. I factor structure and clinical correlates. *Schizophr Res* (2001) **47**(2–3):107–16. doi:10.1016/S0920-9964(00)00035-9
30. Cuesta MJ, Sanchez-Torres AM, de Jalon EG, Campos MS, Ibanez B, Moreno-Izco L, et al. Spontaneous parkinsonism is associated with cognitive impairment in antipsychotic-naive patients with first-episode psychosis: a 6-month follow-up study. *Schizophr Bull* (2014) **40**(5):1164–73. doi:10.1093/schbul/sbt125
31. Lang FU, Kosters M, Lang S, Becker T, Jager M. Psychopathological long-term outcome of schizophrenia – a review. *Acta Psychiatr Scand* (2013) **127**(3):173–82. doi:10.1111/acps.12030
32. Peralta V, Cuesta MJ. The effect of antipsychotic medication on neuromotor abnormalities in neuroleptic-naive nonaffective psychotic patients: a naturalistic study with haloperidol, risperidone, or olanzapine. *Prim Care Companion J Clin Psychiatry* (2010) **12**(2):e1–11. doi:10.4088/PCC.09m00799gry
33. Covington MA, Lunden SL, Cristofaro SL, Wan CR, Bailey CT, Broussard B, et al. Phonetic measures of reduced tongue movement correlate

with negative symptom severity in hospitalized patients with first-episode schizophrenia-spectrum disorders. *Schizophr Res* (2012) **142**(1–3):93–5. doi:10.1016/j.schres.2012.10.005
34. Docx L, Morrens M, Bervoets C, Hulstijn W, Fransen E, De Hert M, et al. Parsing the components of the psychomotor syndrome in schizophrenia. *Acta Psychiatr Scand* (2012) **126**(4):256–65. doi:10.1111/j.1600-0447.2012.01846.x
35. Ungvari GS, Leung SK, Ng FS, Cheung HK, Leung T. Schizophrenia with prominent catatonic features ('catatonic schizophrenia'): I. demographic and clinical correlates in the chronic phase. *Prog Neuropsychopharmacol Biol Psychiatry* (2005) **29**(1):27–38. doi:10.1016/j.pnpbp.2004.08.007
36. Malchow B, Reich-Erkelenz D, Oertel-Knochel V, Keller K, Hasan A, Schmitt A, et al. The effects of physical exercise in schizophrenia and affective disorders. *Eur Arch Psychiatry Clin Neurosci* (2013) **263**(6):451–67. doi:10.1007/s00406-013-0423-2
37. Oertel-Knochel V, Mehler P, Thiel C, Steinbrecher K, Malchow B, Tesky V, et al. Effects of aerobic exercise on cognitive performance and individual psychopathology in depressive and schizophrenia patients. *Eur Arch Psychiatry Clin Neurosci* (2014) **264**(7):589–604. doi:10.1007/s00406-014-0485-9
38. Morrens M, Docx L, Walther S. Beyond boundaries: in search of an integrative view on motor symptoms in schizophrenia. *Front Psychiatry* (2014) **5**:145. doi:10.3389/fpsyt.2014.00145
39. Kaiser S, Heekeren K, Simon JJ. The negative symptoms of schizophrenia: category or continuum? *Psychopathology* (2011) **44**(6):345–53. doi:10.1159/000325912
40. Walther S, Hofle O, Federspiel A, Horn H, Hugli S, Wiest R, et al. Neural correlates of disbalanced motor control in major depression. *J Affect Disord* (2012) **136**(1–2):124–33. doi:10.1016/j.jad.2011.08.020
41. Razavi N, Horn H, Koschorke P, Hugli S, Hofle O, Muller T, et al. Measuring motor activity in major depression: the association between the Hamilton depression rating scale and actigraphy. *Psychiatry Res* (2011) **190**(2–3):212–6. doi:10.1016/j.psychres.2011.05.028
42. Vancampfort D, Probst M, Sweers K, Maurissen K, Knapen J, De Hert M. Relationships between obesity, functional exercise capacity, physical activity participation and physical self-perception in people with schizophrenia. *Acta Psychiatr Scand* (2011) **123**(6):423–30. doi:10.1111/j.1600-0447.2010.01666.x

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Received: 15 October 2014; accepted: 15 December 2014; published online: 05 January 2015.
*Citation: Walther S, Stegmayer K, Horn H, Razavi N, Müller TJ and Strik W (2015) Physical activity in schizophrenia is higher in the first episode than in subsequent ones. Front. Psychiatry **5**:191. doi: 10.3389/fpsyt.2014.00191*
This article was submitted to Schizophrenia, a section of the journal Frontiers in Psychiatry.

frontiers in PSYCHIATRY

ORIGINAL RESEARCH ARTICLE
published: 05 February 2015
doi: 10.3389/fpsyt.2015.00010

The longitudinal course of gross motor activity in schizophrenia – within and between episodes

Sebastian Walther*, Katharina Stegmayer, Helge Horn, Luca Rampa, Nadja Razavi, Thomas J. Müller and Werner Strik

University Hospital of Psychiatry, University of Bern, Bern, Switzerland

Edited by:
Manuel Morrens, University of Antwerp, Belgium

Reviewed by:
Bernhard J. Mitterauer, Volitronics-Institute for Basic Research Psychopathology and Brain Philosophy, Austria
Assen Veniaminov Jablensky, The University of Western Australia, Australia

****Correspondence:***
Sebastian Walther, University Hospital of Psychiatry, University of Bern, Bolligenstrasse 111, Bern 60 3000, Switzerland
e-mail: walther@puk.unibe.ch

Schizophrenia is associated with heterogeneous course of positive and negative symptoms. In addition, reduced motor activity as measured by wrist actigraphy has been reported. However, longitudinal studies of spontaneous motor activity are missing. We aimed to explore whether activity levels were stable within and between psychotic episodes. Furthermore, we investigated the association with the course of negative symptoms. In 45 medicated patients, we investigated motor behavior within a psychotic episode. In addition, we followed 18 medicated patients across 2 episodes. Wrist actigraphy and psychopathological ratings were applied. Within an episode symptoms changed but activity levels did not vary systematically. Activity at baseline predicted the course of negative symptoms. Between two episodes activity recordings were much more stable. Again, activity at the index episode predicted the outcome of negative symptoms. In sum, spontaneous motor activity shares trait and state characteristics, the latter are associated with negative symptom course. Actigraphy may therefore become an important ambulatory instrument to monitor negative symptoms and treatment outcome in schizophrenia.

Keywords: actigraphy, psychosis, negative symptoms, PANSS, avolition

INTRODUCTION

Schizophrenia is characterized by positive symptoms, negative symptoms, and disorganization. Furthermore, cognitive and motor symptoms have been identified as relevant symptom clusters of schizophrenia. In fact, the current DSM5 concept of psychoses proposed eight dimensions of psychopathology to be assessed in subjects with schizophrenia, including motor symptoms (1). Schizophrenia is further associated with particular heterogeneity in course and outcome (2, 3). Generally, symptoms ameliorate during the course of a psychotic episode; however, negative symptoms do not respond as well to treatment as positive symptoms and disorganization too (4, 5). In longitudinal studies over years, negative symptoms generally tend to be stable (5, 6). However, findings of a recent meta-analysis suggest that negative symptoms may improve to a greater extent than what has previously been assumed (7).

Motor signs in schizophrenia include catatonia, neurological soft signs, psychomotor slowing, and extrapyramidal symptoms, i.e., abnormal involuntary movements, akathisia, and parkinsonism (8, 9). These motor symptoms are prevalent throughout the course of the disorder and may be affected by antipsychotic treatment. Particularly, gross motor behavior is important in schizophrenia; it is linked with medication, symptom dimensions, and relevant for physical health (10, 11). Spontaneous motor activity may be objectively assessed with continuous wrist actigraphy (12). A number of parameters can be calculated from actigraphy data, such as the activity level (AL; activity counts per hour), the movement index (MI; percentage of active periods), or the average duration of immobility periods (12). However, it was the AL that was associated with negative syndrome severity (13–15) and neuroimaging markers (16–18). In general, schizophrenia patients have reduced levels of daytime activity compared to healthy control subjects (15, 17, 19, 20). One study performed actigraphic recordings for seven consecutive days (19). Their graphs indicate rather stable measurements throughout a week, even though no statistical test had been applied to explore temporal fluctuations. Actigraphy has been used for cross-sectional comparisons of spontaneous motor behavior in schizophrenia; however, no study has addressed the longitudinal course within or even between psychotic episodes. Studies on motor abnormalities in first episode and chronic schizophrenia indicate that most motor symptoms including hypokinesia are attenuated by antipsychotic treatment within 4 weeks (21, 22). Therefore, we could assume that spontaneous motor activity is subject to changes within an episode. The longitudinal course of motor signs over more than a few weeks has only rarely been addressed. Few longitudinal studies included finger tapping and found no changes over time (23). Docx et al. report amelioration of catatonia and neurological soft signs in stable patients over 1 year (24). Likewise, neurological soft signs tend to decrease within the first year in schizophrenia (25).

The current study aimed at testing whether spontaneous motor activity would change during the course of a psychotic episode as well as during the course between two psychotic episodes. Furthermore, we wanted to investigate whether spontaneous motor activity at baseline would predict the course of symptoms in schizophrenia. The literature suggests wide distribution of activity levels between subjects with schizophrenia (15, 17). We hypothesized that a considerable proportion of the variance was stable over

time (trait motor activity) and that some of the variable motor activity was state dependent and linked to negative symptoms of schizophrenia.

MATERIALS AND METHODS

PARTICIPANTS

Participants were recruited from the inpatient and outpatient department of the University Hospital of Psychiatry, Bern, Switzerland. This investigation includes data from three different studies that all used the same actigraphy procedures. Diagnoses were given after thorough clinical examination and review of all case files by board certified psychiatrists. The local mental health care system ensures that most of the patients are admitted to our clinic in every psychotic episode requiring inpatient treatment, allowing the collection of reliable diagnostic information. In a proportion of studies that contributed data to this analysis, the diagnoses were ascertained by structured clinical interviews (both SCID and MINI; 27% of cases). Patients were excluded in case of substance abuse other than nicotine, medical conditions affecting physical activity (e.g., injuries such as fractures or ligament ruptures and conditions such as idiopathic parkinsonism, arthrosis, or rheumatism) and epilepsy. Physical activity was recorded approximately 2 weeks after admission to the psychiatric department (24 h at each assessment time point). At the same time, psychopathology was assessed using the positive and negative syndrome scale (PANSS) (20). In the within-episode sample, actigraphy and PANSS assessments were repeated after the acute symptoms had been alleviated. In the between episodes sample, assessments were repeated within the first 2 weeks of the subsequent inpatient treatment due to a psychotic episode. Episode and inter-episode interval have been defined according the practice guidelines developed by the American Psychiatric Association codified a three-phase model of schizophrenia disease course, with the recognition that these phases "merge into one another without absolute, clear boundaries between them" (26). According to this model, the "acute phase," characterized by florid psychosis and severe positive and/or negative symptoms, which is followed by a "stabilization phase," during which symptoms recede and decrease in severity, and a subsequent "stable phase" with reduced symptom severity and relative symptom stability. In detail, the stable phase reflects the inter-episode interval while the acute phase including the stabilization phase has been defined as episode and within-episode interval (26, 27). Chlorpromazine equivalents (CPZ) of the current antipsychotic pharmacotherapy were calculated according to Woods (21). The protocols of the studies applying wrist actigraphy in schizophrenia spectrum disorders had been approved by the local ethics committee and participants provided written informed consent prior to study inclusion.

Within-episodes sample

In total, 45 patients (28 men and 15 women) were included with an average period between measurements of 42 days. Mean age was 36.9 ± 9.5 years, mean duration of illness 11.1 ± 10.7 years. Patients experienced 6.8 ± 6.6 episodes. The majority was treated with antipsychotics (94%; aripiprazole, clozapine, quetiapine, risperidone, olanzapine, haloperidol, amisulpride, zuclopenthixol, and flupenthixol), most of them atypical (91%).

Between episodes sample

In total, 18 patients (13 men and 5 women) were included with an average period between episodes of 639 days (4 subjects of the within-episode sample were also included in the between episode sample). Mean age was 34.7 ± 10.5 years, mean duration of illness 8.7 ± 8.0 years. Patients experienced 6.9 ± 7.2 episodes. All patients received antipsychotic treatment (aripiprazole, clozapine, quetiapine, risperidone, olanzapine, haloperidol, and amisulpride) with predominantly atypical antipsychotics (index episode 83%, later episode 94%).

ACTIGRAPHY

Participants wore an actigraph (Actiwatch, Cambridge Neurotechnology, Inc., Cambridge, UK) for 24 consecutive hours at the wrist of the non-dominant arm. The piezoelectronic sensor converts acceleration into movement counts. Data were sampled in 2 s intervals. Participants provided sleep log information and information on recording pauses (due to showering or bathing). Only the data collected during wakeful periods of the 24 h recording time were analyzed. Activity counts were averaged to provide the AL in counts/h.

STATISTICAL ANALYSES

Positive and negative syndrome scale scores were used to calculate two factors of negative symptoms as in previous studies (15, 28, 29): the expressivity factor including items N1 (blunted affect) and N6 (lack of spontaneity and flow of conversation) and the avolition factor including items N2 (emotional withdrawal) and N4 (passive/apathetic social withdrawal). Longitudinal comparisons of clinical and actigraphic parameters were calculated using paired *T*-tests. To test the explained variance, we entered AL baseline as predictor of a linear regression model of AL post. In both cohorts, we detected wide variability of AL changes. Using Pearson correlations, we explored associations between AL at baseline and clinical parameters at baseline and in the longitudinal course. Next, we aimed at testing groups according to their baseline AL values. In order to test the longitudinal course of PANSS scores according to baseline motor activity, we defined groups applying the 33rd and 66th percentile of the baseline AL in both cohorts. Group comparisons (low, medium, and high AL) were conducted using repeated measures ANOVAs. *Post hoc* analyses were Sidak corrected for multiple comparisons. All analyses were conducted with SPSS22.

RESULTS

WITHIN EPISODES

Within psychotic episodes longitudinal AL changes were wide-ranged. Paired *T*-tests of AL baseline and AL post indicated no change (see **Table 1**). However, only 28% of the patients had stable AL, i.e., AL changed by <20%. AL post ranged 35–272% of the AL at baseline. In contrast, PANSS positive and PANSS total scores were attenuated, a trend for improvement was detected in PANSS negative scores (see **Table 1**). Interestingly, baseline AL inversely correlated at trend level with% of change of activity ($r = -0.286$; $p = 0.063$), indicating that the less patients move at baseline the more likely AL changes within episodes. However, the magnitude of change from baseline AL was not predictive of the longitudinal course of PANSS scores (*r*-range: −0.17–0.10).

Table 1 | Paired *T*-tests within episode.

	Baseline	Post	*T*	df	*p*	*r*
AL (counts/h)	13735 ± 7274	13544 ± 8128	0.2	42	0.870	0.52
PANSS positive	17.1 ± 5.8	13.1 ± 4.8	4.3	42	<0.001	0.34
PANSS negative	18.4 ± 6.8	16.4 ± 6.2	1.7	42	0.099	0.30
PANSS avolition	5.3 ± 2.2	4.9 ± 2.4	0.8	42	0.406	0.10
PANSS expressivity	5.5 ± 3.0	5.0 ± 2.3	1.4	42	0.181	0.56
PANSS total	69.5 ± 16.6	59.0 ± 15.9	3.4	42	0.001	0.24
CPZ (mg)	543 ± 401	531 ± 435	0.2	42	0.807	0.69

Table 2 | Repeated measures ANOVAs within episode.

		AL baseline group			Time		Group		Time × group	
		Low	Medium	High	*F*	*p*	*F*	*p*	*F*	*p*
AL	Baseline	7742 ± 1178	11077 ± 1469	22577 ± 6016	0.3	0.863	47.2	<0.001	0.8	0.455
	Post	9096 ± 4684	11329 ± 4174	20366 ± 9781						
PANSS positive	Baseline	14.5 ± 4.9	19.5 ± 6.1	17.3 ± 5.7	17.7	<0.001	5.1	0.011	0.03	0.967
	Post	10.8 ± 3.6	15.3 ± 5.0	13.0 ± 4.8						
PANSS negative	Baseline	21.9 ± 6.9	19.3 ± 5.6	13.9 ± 5.7	3.3	0.078	4.1	0.025	3.5	0.039
	Post	15.8 ± 5.7	18.5 ± 7.4	14.8 ± 5.2						
PANSS avolition	Baseline	6.2 ± 2.6	5.6 ± 1.9	4.1 ± 1.6	0.9	0.357	1.5	0.230	4.5	0.017
	Post	4.0 ± 2.3	5.7 ± 2.4	5.0 ± 2.3						
PANSS expressivity	Baseline	7.5 ± 3.0	5.3 ± 2.8	3.7 ± 2.0	2.3	0.134	5.2	0.010	4.8	0.014
	Post	5.4 ± 2.2	5.5 ± 2.7	3.9 ± 1.9						
PANSS total	Baseline	69.8 ± 12.9	76.9 ± 20.5	61.4 ± 11.7	11.9	0.001	4.6	0.016	1.1	0.339
	Post	53.6 ± 15.4	66.2 ± 16.0	56.6 ± 14.3						

AL: high > low ($p < 0.001$) and high > medium ($p < 0.001$) post hoc Sidak tests.

Activity level at baseline predicted AL post ($R^2 = 0.26, F = 15.0, p < 0.001$). AL baseline correlated with PANSS negative baseline ($r = -0.53, p < 0.001$). Furthermore, AL post correlated with PANSS negative at both time points (PANSS negative baseline: $r = -0.39, p = 0.011$; PANSS negative post: $r = -0.35, p = 0.021$). Therefore, we explored whether AL baseline would indicate longitudinal changes in psychopathology. AL baseline was used to define three groups based on percentile rankings (33rd and 66th percentiles), i.e., low, medium, and high AL baseline. The three patient groups did not differ in terms of age ($F = 1.3$, df = 2, $p = 0.294$), duration of illness ($F = 1.4$, df = 2, $p = 0.258$), number of episodes ($F = 1.2$, df = 2, $p = 0.311$), CPZ ($F = 0.01$, df = 2, $p = 0.992$), and the time between measurements ($F = 0.5$, df = 2, $p = 0.609$). Time effects were strong for PANSS positive and total scores, indicating attenuation of symptoms during the episode (see **Table 2**; **Figure 1**). Significant group × time interactions were detected only for the measures of the negative syndrome: PANSS negative scores, avolition, and expressivity scores decreased significantly only in the group with low AL at baseline ($T = 3.4$, $p = 0.005$; $T = 2.7$, $p = 0.019$; $T = 3.2$, $p = 0.006$), while in the other groups negative syndrome scores remained stable.

BETWEEN EPISODES

Between episodes, AL was more stable than within episodes. In fact, 50% of the patients had AL changes of ±20%. AL at the later episode ranged 40–167% of AL at the index episode. Likewise, PANSS scores were similar between episodes (see **Table 3**), except a trend for deterioration in the PANSS avolition score. AL at index episode predicted AL at the later episode ($R^2 = 0.65$, $F = 30.0$, $p < 0.001$). Neither AL at index episode nor AL at a later episode correlated significantly with PANSS scores. Still, when the group was divided according to AL at index episode (low, medium, high AL), we detected a significant group effect on PANSS negative scores, as well as a trend to a time × group interaction (see **Table 4**; **Figure 2**). Negative syndrome scores increased between episodes in patients with high AL at index episode ($T = -2.6$, $p = 0.047$) and at trend level also in patients with low AL at index episode ($T = -2.1, p = 0.095$). Likewise, avolition scores increased at trend level in the group with high AL at index episode ($T = -2.7$, $p = 0.052$). In the group with low AL at index episode, we found single PANSS negative items to increase over time at trend level: N1 (blunted affect, $p = 0.076$) and N3 (poor rapport, $p = 0.076$). In the group with high AL at index episode, we found trends for changes of the items N2 (emotional withdrawal, $p = 0.070$) and N6 (lack of spontaneity, $p = 0.070$).

DISCUSSION

The present study explored the longitudinal course of spontaneous motor activity in schizophrenia. Results indicate considerable variance within psychotic episodes and stability of activity levels

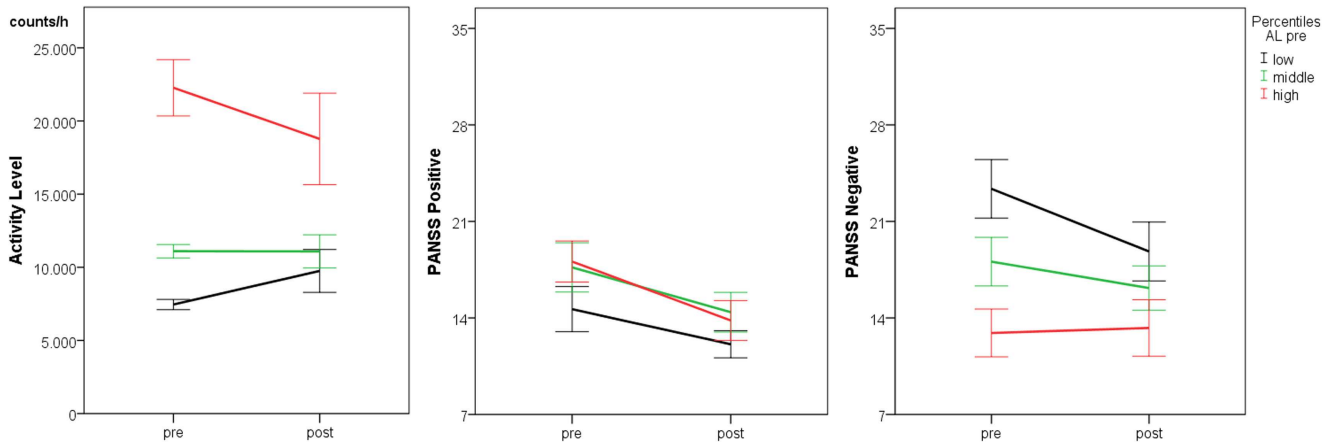


FIGURE 1 | Within-episode course of activity and psychopathology ($n = 45$) lines indicate mean ± SE.

Table 3 | Paired *T*-tests between episodes.

	Index episode	Later episode	*T*	df	*p*	*r*
AL (counts/h)	15472 ± 10152	13591 ± 7474	1.3	17	0.203	0.81
PANSS positive	13.3 ± 5.1	14.6 ± 6.0	−1.4	17	0.183	0.77
PANSS negative	17.7 ± 7.6	19.6 ± 7.7	−1.1	17	0.274	0.67
PANSS avolition	4.1 ± 2.0	5.5 ± 3.2	−2.1	17	0.051	0.53
PANSS expressivity	5.5 ± 3.1	6.1 ± 2.9	−1.0	17	0.351	0.69
PANSS total	60.0 ± 16.1	65.4 ± 16.1	−1.2	17	0.253	0.29
CPZ (mg)	440 ± 305	608 ± 387	−1.8	17	0.092	0.36

Table 4 | Repeated measures ANOVA between episodes ($n = 18$).

		AL index group			Time		Group		Time × group	
		Low	Medium	High	*F*	*p*	*F*	*p*	*F*	*p*
AL	Index	6870 ± 1669	13241 ± 2623	26305 ± 10256	2.4	0.143	13.0	0.001	4.1	0.038
	Later	7263 ± 3211	14016 ± 4016	19495 ± 8567						
PANSS positive	Index	15.5 ± 7.3	11.8 ± 3.8	12.7 ± 3.6	1.9	0.189	0.7	0.522	0.86	0.442
	Later	15.8 ± 5.4	12.3 ± 6.4	15.7 ± 6.7						
PANSS negative	Index	17.7 ± 7.9	17.2 ± 7.4	18.2 ± 8.9	1.6	0.231	4.1	0.025	2.9	0.088
	Later	22.0 ± 9.3	14.3 ± 2.3	21.7 ± 8.1						
PANSS avolition	Index	4.7 ± 2.7	4.0 ± 2.0	3.4 ± 0.9	4.8	0.047	0.6	0.539	1.7	0.217
	Later	6.3 ± 4.1	3.8 ± 2.0	6.2 ± 2.7						
PANSS expressivity	Index	5.5 ± 2.9	5.8 ± 3.0	5.2 ± 3.8	0.8	0.396	0.1	0.880	1.4	0.273
	Later	7.0 ± 3.6	5.0 ± 1.2	6.0 ± 3.4						
PANSS total	Index	62.3 ± 17.9	55.3 ± 17.5	62.3 ± 15.3	1.3	0.275	1.5	0.264	0.3	0.751
	Later	69.5 ± 15.4	55.7 ± 13.7	71.0 ± 16.9						

AL: high > low ($p < 0.001$) and high > medium ($p = 0.028$) post hoc Sidak tests.

between episodes. Furthermore, within-episodes baseline activity predicted the outcome of negative symptom severity. Therefore, our hypotheses were confirmed: spontaneous motor activity in schizophrenia has trait and state characteristics; the latter are associated with the negative syndrome.

WITHIN-EPISODE VARIANCE

Activity levels for the whole group demonstrated considerable variance, only 26% of the variance of AL post were predicted by AL at baseline. When we split the sample into three similar sized groups according to the baseline AL, we found no changes

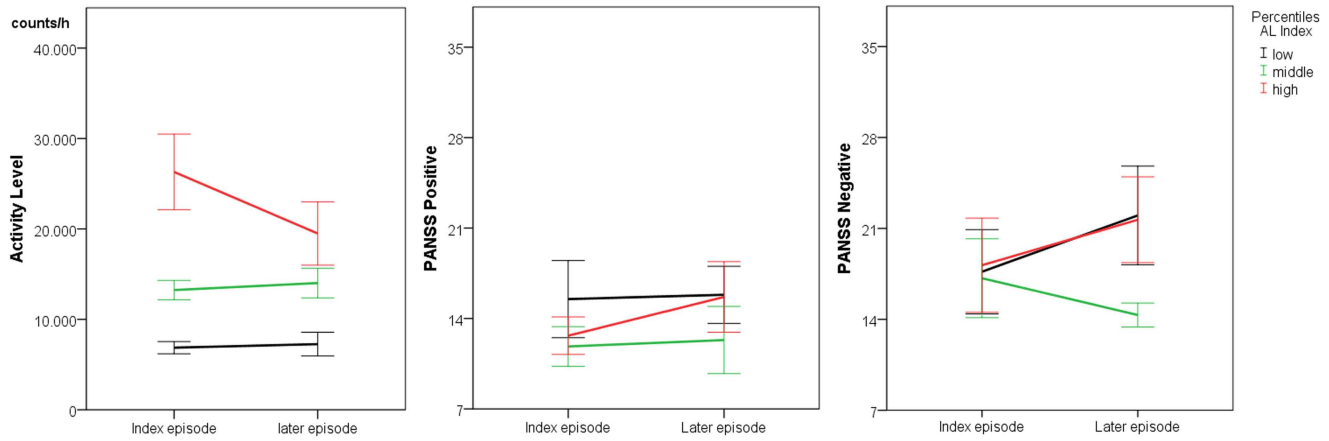


FIGURE 2 | Between episode course of activity and psychopathology ($n = 18$) lines indicate mean ± SE.

over time; instead, group differences remained throughout the episode. This stability of motor activity is congruent with the observations over 1 week (19). However, other motor signs in schizophrenia are attenuated by antipsychotic treatment. This is true for abnormal involuntary movements and neurological soft signs but also for hypokinesia, parkinsonism, and catatonia (21, 22, 25). Particularly, when hypokinetic movement disorders were ameliorated, we could expect an increase in AL within an episode. Our findings fail to support this notion. As noted above, there was considerable variance in the longitudinal course of AL within an episode. Peralta and Cuesta reported in their sample of 100 unmedicated first episode patients that 21% had parkinsonism and 18% catatonia at baseline (30). The two hypokinetic movement disorders demonstrated distinct courses with antipsychotic treatment; parkinsonism increased and catatonia declined within 4 weeks. Interestingly, for both syndromes, cases were identified who had drug emergent, drug responsive, and drug irresponsive courses (30). Therefore, patients can present with very different courses of movement disorders, which may explain our finding of stable AL in the paired T-test and only 26% of explained variance between assessments.

Activity level at baseline separated the groups according to negative syndrome severity. As in previous studies, lower AL was associated with increased negative syndrome scores (13–15). Furthermore, the groups differed in the course of negative syndrome. Patients in the low AL group experienced a pronounced decrease of negative syndrome scores within the episode, while the other groups did not. This finding was true for both, the avolition and the expressivity component of the PANSS negative syndrome score. Baseline AL may therefore predict who will have a higher probability of reduced negative symptoms with treatment. In line with the literature, within episodes in general PANSS positive and total scores decreased more than negative scores with antipsychotic treatment (4, 5, 31). In contrast, the avolition score remained stable (5, 32). Therefore, avolition may represent the invariant component of negative symptoms while other negative symptoms tend to improve (32). Interestingly, specifically deficits of "action-orientation" (slowing of the initiation of fine motor movements) have been associated with avolition (29). Likewise, problems of initiation of goal directed behavior might have led to psychomotor slowing in our study. Avolition is a critical component of the negative syndrome in schizophrenia, linked to impaired motivation and poor functional outcome (33). Measures of avolition are correlated with reduced AL in schizophrenia (15, 34). Because actigraphy is a well-accepted, ambulatory, and non-invasive way of obtaining objective data on spontaneous movement, it should be applied in larger pharmaceutical trials on negative symptoms in schizophrenia. At the very least, it could help to identify subjects at baseline with increased likelihood of responding to treatments for negative symptoms.

BETWEEN EPISODES STABILITY

Between two psychotic episodes AL was much more stable (65% explained variance) than within an episode. The time × group interaction indicated regression to the mean for AL in the longitudinal course. Our results argue for a trait component in AL in schizophrenia. Data on the long-term course of other motor phenomena are scarce and produced mixed results. Studies on neurological soft signs found subjects with increasing and subjects with decreasing symptoms (24, 25). The patients with increasing soft signs had poorer overall outcome (25). Catatonia was found to be reduced within 1 year even in chronic schizophrenia, but parkinsonism and motor retardation were unchanged (24). In contrast, cross-sectional reports of motor function in schizophrenia (chronic vs. first episode) noted generalized deterioration with ongoing course (35). Still, longitudinal studies of motor behavior during multiple episodes are missing.

Long-term studies starting in the first psychotic episodes indicate that considerable proportions of negative symptoms remain unchanged over several years (5, 6, 32). Again, avolition was most stable among the negative symptoms (5, 32). In our study, both positive and negative symptom scores displayed no time effect in the whole group, which may be accounted for by the small sample size. Still, correlations between index and later episode were strong for both syndromes. However, the avolition score indicated overall deterioration of this component of negative

symptoms. In patients with high AL at baseline, single PANSS negative items emotional withdrawal (N2) and lack of spontaneity (N6) indicated deterioration at trend level in this group. Again, we noted an effect of AL on negative syndrome scores with a significant group effect and a group × time interaction at trend level. Here, patients with higher AL at index episode increased their negative syndrome scores between episodes. This is particularly interesting as the negative syndrome scores at baseline were similar between groups. Thus, only our measure of spontaneous motor activity had predictive value for negative syndrome scores. Again, results must be interpreted with caution due to the small groups.

LIMITATIONS

This was a truly naturalistic study design, which is not able to detect longitudinal changes associated with specific drug effects. There are various effects that may have contributed to the observed changes. Medication may have heterogeneous effects on motor activity (36). The observation period could not be standardized. In addition, the sample sizes were small, particularly for the inter-episode comparison. Thus, we may have missed effects due to type-II errors. In addition, diagnoses were given after thorough clinical psychiatric examination and chart review; however, structured clinical interviews (both SCID and MINI) were only applied in a proportion of (27% of cases) patients. We assessed negative symptoms with the PANSS negative syndrome scale and PANSS factors for avolition and expressivity. Additional negative scales such as the scale for the assessment of negative symptoms (SANS) (37) or the clinical assessment interview for negative symptoms (CAINS) (38) were not applied. Finally, future studies could include measures of motor syndromes such as catatonia, neurological soft signs, and parkinsonism to account for differential effects of medication on motor signs (30). In sum, we think our results are encouraging for large randomized controlled trials focusing on negative symptoms in schizophrenia.

CONCLUSION

Spontaneous gross motor behavior in schizophrenia shares trait and state characteristics. Within-episodes motor activity varies with negative syndrome scores, while between psychotic episodes motor activity remains stable. Wrist actigraphy should be considered as objective ambulatory non-invasive instrument to monitor the effects of treatment on negative symptoms.

AUTHOR CONTRIBUTIONS

SW and HH designed the study. SW wrote the protocol. LR, NR, KS, and SW recruited participants and performed assessments. SW performed the data analyses. All authors interpreted and discussed the findings. SW wrote the first draft of the manuscript. All authors contributed to the final version of the manuscript.

REFERENCES

1. Heckers S, Barch DM, Bustillo J, Gaebel W, Gur R, Malaspina D, et al. Structure of the psychotic disorders classification in DSM-5. *Schizophr Res* (2013) **150**(1):11–4. doi:10.1016/j.schres.2013.04.039
2. van Os J, Kapur S. Schizophrenia. *Lancet* (2009) **374**(9690):635–45. doi:10.1016/S0140-6736(09)60995-8
3. Insel TR. Rethinking schizophrenia. *Nature* (2010) **468**(7321):187–93. doi:10.1038/nature09552
4. Addington J, Addington D. Positive and negative symptoms of schizophrenia. Their course and relationship over time. *Schizophr Res* (1991) **5**(1):51–9. doi:10.1016/0920-9964(91)90039-T
5. Arndt S, Andreasen NC, Flaum M, Miller D, Nopoulos P. A longitudinal study of symptom dimensions in schizophrenia. Prediction and patterns of change. *Arch Gen Psychiatry* (1995) **52**(5):352–60. doi:10.1001/archpsyc.1995.03950170026004
6. Lang FU, Kosters M, Lang S, Becker T, Jager M. Psychopathological long-term outcome of schizophrenia – a review. *Acta Psychiatr Scand* (2013) **127**(3):173–82. doi:10.1111/acps.12030
7. Savill M, Banks C, Khanom H, Priebe S. Do negative symptoms of schizophrenia change over time? A meta-analysis of longitudinal data. *Psychol Med* (2014):1–15. doi:10.1017/S0033291714002712
8. Morrens M, Docx L, Walther S. Beyond boundaries: in search of an integrative view on motor symptoms in schizophrenia. *Front Psychiatry* (2014) **5**:145. doi:10.3389/fpsyt.2014.00145
9. Walther S, Strik W. Motor symptoms and schizophrenia. *Neuropsychobiology* (2012) **66**(2):77–92. doi:10.1159/000339456
10. Brown S, Birtwistle J, Roe L, Thompson C. The unhealthy lifestyle of people with schizophrenia. *Psychol Med* (1999) **29**(3):697–701. doi:10.1017/S0033291798008186
11. Vancampfort D, Probst M, Sweers K, Maurissen K, Knapen J, De Hert M. Relationships between obesity, functional exercise capacity, physical activity participation and physical self-perception in people with schizophrenia. *Acta Psychiatr Scand* (2011) **123**(6):423–30. doi:10.1111/j.1600-0447.2010.01666.x
12. Middelkoop HA, van Dam EM, Smilde-van den Doel DA, Van Dijk G. 45-hour continuous quintuple-site actimetry: relations between trunk and limb movements and effects of circadian sleep-wake rhythmicity. *Psychophysiology* (1997) **34**(2):199–203. doi:10.1111/j.1469-8986.1997.tb02132.x
13. Walther S, Koschorke P, Horn H, Strik W. Objectively measured motor activity in schizophrenia challenges the validity of expert ratings. *Psychiatry Res* (2009) **169**(3):187–90. doi:10.1016/j.psychres.2008.06.020
14. Walther S, Ramseyer F, Horn H, Strik W, Tschacher W. Less structured movement patterns predict severity of positive syndrome, excitement, and disorganization. *Schizophr Bull* (2014) **40**(3):585–91. doi:10.1093/schbul/sbt038
15. Docx L, Sabbe B, Provinciael P, Merckx N, Morrens M. Quantitative psychomotor dysfunction in schizophrenia: a loss of drive, impaired movement execution or both? *Neuropsychobiology* (2013) **68**(4):221–7. doi:10.1159/000355293
16. Walther S, Federspiel A, Horn H, Razavi N, Wiest R, Dierks T, et al. Resting state cerebral blood flow and objective motor activity reveal basal ganglia dysfunction in schizophrenia. *Psychiatry Res* (2011) **192**(2):117–24. doi:10.1016/j.pscychresns.2010.12.002
17. Walther S, Federspiel A, Horn H, Razavi N, Wiest R, Dierks T, et al. Alterations of white matter integrity related to motor activity in schizophrenia. *Neurobiol Dis* (2011) **42**(3):276–83. doi:10.1016/j.nbd.2011.01.017
18. Bracht T, Schnell S, Federspiel A, Razavi N, Horn H, Strik W, et al. Altered cortico-basal ganglia motor pathways reflect reduced volitional motor activity in schizophrenia. *Schizophr Res* (2013) **143**(2–3): 269–76. doi:10.1016/j.schres.2012.12.004
19. Wichniak A, Skowerska A, Chojnacka-Wojtowicz J, Taflinski T, Wierzbicka A, Jernajczyk W, et al. Actigraphic monitoring of activity and rest in schizophrenic patients treated with olanzapine or risperidone. *J Psychiatr Res* (2011) **45**(10):1381–6. doi:10.1016/j.jpsychires.2011.05.009
20. Berle JO, Hauge ER, Oedegaard KJ, Holsten F, Fasmer OB. Actigraphic registration of motor activity reveals a more structured behavioural pattern in schizophrenia than in major depression. *BMC Res Notes* (2010) **3**:149. doi:10.1186/1756-0500-3-149
21. Peralta V, Campos MS, De Jalon EG, Cuesta MJ. Motor behavior abnormalities in drug-naive patients with schizophrenia spectrum disorders. *Mov Disord* (2010) **25**(8):1068–76. doi:10.1002/mds.23050
22. Peralta V, Cuesta MJ. Motor features in psychotic disorders. I. Factor structure and clinical correlates. *Schizophr Res* (2001) **47**(2–3):107–16. doi:10.1016/S0920-9964(00)00035-9
23. Hoff AL, Svetina C, Shields G, Stewart J, DeLisi LE. Ten year longitudinal study of neuropsychological functioning subsequent to a first episode of schizophrenia. *Schizophr Res* (2005) **78**(1):27–34. doi:10.1016/j.schres.2005.05.010

24. Docx L, Sabbe B, Fransen E, Bervoets C, Hulstijn W, Van den Bossche B, et al. Longitudinal evaluation of the psychomotor syndrome in schizophrenia. *J Neuropsychiatry Clin Neurosci* (Forthcoming). doi:10.1111/j.1600-0447.2012.01846.x
25. Bachmann S, Bottmer C, Schroder J. Neurological soft signs in first-episode schizophrenia: a follow-up study. *Am J Psychiatry* (2005) **162**(12):2337–43. doi:10.1176/appi.ajp.162.12.2337
26. American Psychiatric Association. Practice guideline for the treatment of patients with schizophrenia. *Am J Psychiatry* (1997) **154**(4 Suppl):1–63. doi:10.1176/ajp.154.4.1
27. Andreasen NC, Carpenter WT Jr, Kane JM, Lasser RA, Marder SR, Weinberger DR. Remission in schizophrenia: proposed criteria and rationale for consensus. *Am J Psychiatry* (2005) **162**(3):441–9. doi:10.1176/appi.ajp.162.3.441
28. Van den Oord EJCG, Rujescu D, Robles JR, Giegling I, Birrell C, Bukszar J, et al. Factor structure and external validity of the PANSS revisited. *Schizophr Res* (2006) **82**(2–3):213–23. doi:10.1016/j.schres.2005.09.002
29. Bervoets C, Docx L, Sabbe B, Vermeylen S, Van Den Bossche MJ, Morsel A, et al. The nature of the relationship of psychomotor slowing with negative symptomatology in schizophrenia. *Cogn Neuropsychiatry* (2014) **19**(1):36–46. doi:10.1080/13546805.2013.779578
30. Peralta V, Cuesta MJ. The effect of antipsychotic medication on neuromotor abnormalities in neuroleptic-naive nonaffective psychotic patients: a naturalistic study with haloperidol, risperidone, or olanzapine. *Prim Care Companion J Clin Psychiatry* (2010) **12**(2). doi:10.4088/PCC.09m00799gry
31. Peralta V, Cuesta MJ, Martinez-Larrea A, Serrano JF. Patterns of symptoms in neuroleptic-naive patients with schizophrenia and related psychotic disorders before and after treatment. *Psychiatry Res* (2001) **105**(1–2):97–105. doi:10.1016/S0165-1781(01)00319-5
32. Ucok A, Ergul C. Persistent negative symptoms after first episode schizophrenia: a 2-year follow-up study. *Schizophr Res* (2014) **158**(1–3):241–6. doi:10.1016/j.schres.2014.07.021
33. Foussias G, Remington G. Negative symptoms in schizophrenia: avolition and Occam's razor. *Schizophr Bull* (2010) **36**(2):359–69. doi:10.1093/schbul/sbn094
34. Farrow TF, Hunter MD, Wilkinson ID, Green RD, Spence SA. Structural brain correlates of unconstrained motor activity in people with schizophrenia. *Br J Psychiatry* (2005) **187**:481–2. doi:10.1192/bjp.187.5.481
35. Sponheim SR, Jung RE, Seidman LJ, Mesholam-Gately RI, Manoach DS, O'Leary DS, et al. Cognitive deficits in recent-onset and chronic schizophrenia. *J Psychiatr Res* (2010) **44**(7):421–8. doi:10.1016/j.jpsychires.2009.09.010
36. Walther S, Horn H, Razavi N, Koschorke P, Wopfner A, Muller TJ, et al. Higher motor activity in schizophrenia patients treated with olanzapine versus risperidone. *J Clin Psychopharmacol* (2010) **30**(2):181–4. doi:10.1097/JCP.0b013e3181d2ef6f
37. Andreasen NC. The scale for the assessment of negative symptoms (SANS): conceptual and theoretical foundations. *Br J Psychiatry Suppl* (1989) (7):49–58.
38. Forbes C, Blanchard JJ, Bennett M, Horan WP, Kring A, Gur R. Initial development and preliminary validation of a new negative symptom measure: the clinical assessment interview for negative symptoms (CAINS). *Schizophr Res* (2010) **124**(1–3):36–42. doi:10.1016/j.schres.2010.08.039

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Received: 29 October 2014; accepted: 21 January 2015; published online: 05 February 2015.

*Citation: Walther S, Stegmayer K, Horn H, Rampa L, Razavi N, Müller TJ and Strik W (2015) The longitudinal course of gross motor activity in schizophrenia – within and between episodes. Front. Psychiatry **6**:10. doi: 10.3389/fpsyt.2015.00010*

This article was submitted to Schizophrenia, a section of the journal Frontiers in Psychiatry.

frontiers in PSYCHIATRY

ORIGINAL RESEARCH ARTICLE
published: 06 January 2015
doi: 10.3389/fpsyt.2014.00189

Preserved learning during the symbol–digit substitution test in patients with schizophrenia, age-matched controls, and elderly

Claudia Cornelis[1,2]*, Livia J. De Picker[1,2], Wouter Hulstijn[1,3], Glenn Dumont[1,2], Maarten Timmers[4], Luc Janssens[4], Bernard G. C. Sabbe[1,2] and Manuel Morrens[1,5]

[1] Collaborative Antwerp Psychiatric Research Institute, University of Antwerp, Antwerp, Belgium
[2] University Psychiatric Center St. Norbertushuis, Duffel, Belgium
[3] Donders Institute for Brain, Cognition and Behaviour, Radboud University Nijmegen, Nijmegen, Netherlands
[4] Janssen Research and Development, Janssen Pharmaceutica N.V., Beerse, Belgium
[5] Psychiatric Hospital Broeders Alexianen, Boechout, Belgium

Edited by:
Sebastian Walther, University Hospital of Psychiatry, Switzerland

Reviewed by:
Katharina Stegmayer, University Hospital of Psychiatry, Switzerland
Benny Liberg, Karolinska Institutet, Sweden

***Correspondence:**
Claudia Cornelis, Collaborative Antwerp Psychiatric Institute (CAPRI), University of Antwerp, Campus Drie Eiken, Universiteitsplein 1, Antwerp B-2610, Belgium
e-mail: claudia.cornelis@uantwerpen.be

Objective: Speed of processing, one of the main cognitive deficits in schizophrenia is most frequently measured with a digit–symbol-coding test. Performance on this test is additionally affected by writing speed and the rate at which symbol–digit relationships are learned, two factors that may be impaired in schizophrenia. This study aims to investigate the effects of sensorimotor speed, short-term learning, and long-term learning on task performance in schizophrenia. In addition, the study aims to explore differences in learning effects between patients with schizophrenia and elderly individuals.

Methods: Patients with schizophrenia ($N = 30$) were compared with age-matched healthy controls ($N = 30$) and healthy elderly volunteers ($N = 30$) during the Symbol–Digit Substitution Test (SDST). The task was administered on a digitizing tablet, allowing precise measurements of the time taken to write each digit (writing time) and the time to decode symbols into their corresponding digits (matching time). The SDST was administered on three separate days (day 1, day 2, day 7). Symbol–digit repetitions during the task represented short-term learning and repeating the task on different days represented long-term learning.

Results: The repetition of the same symbol–digit combinations within one test and the repetition of the test over days resulted in significant decreases in matching time. Interestingly, these short-term and long-term learning effects were about equal among the three groups. Individual participants showed a large variation in the rate of short-term learning. In general, patients with schizophrenia had the longest matching time whereas the elderly had the longest writing time. Writing time remained the same over repeated testing.

Conclusion: The rate of learning and sensorimotor speed was found to have a substantial influence on the SDST score. However, a large individual variation in learning rate should be taken into account in the interpretation of task scores for processing speed. Equal learning rates among the three groups suggest that unintentional learning in schizophrenia and in the elderly is preserved. These findings are important for the design of rehabilitation programs for schizophrenia.

Keywords: symbol–digit substitution test, coding task, processing speed, implicit learning, schizophrenia

INTRODUCTION

Schizophrenia is a psychiatric disorder, characterized by positive symptoms (e.g., hallucinations and delusions), negative symptoms (e.g., avolition and reduced emotional expressivity), and severe cognitive disabilities. Since cognitive deficits in schizophrenia are significantly correlated to poor functional outcomes (1) and quality of life (2), the development of pharmacological and remediation techniques addressing these impairments could be highly beneficial to the clinical outcome.

Cognition is not a single entity but can be divided into several domains. In schizophrenia research, the areas of primary interest are: processing speed, attention/vigilance, working memory, verbal learning, visual learning, executive functioning and social cognition (3). The combination of these domains may contribute

differently to the overall clinical picture of cognitive decline in schizophrenia. Experimental tasks that focus on isolating the relative influence of these specific cognitive domains are needed to specify which deficits are most pronounced in order to provide a targeted treatment.

Processing speed has been shown to be a very distinguishing and reliable factor to characterize cognitive deficits in schizophrenia (4). This parameter reflects the speed with which different cognitive and sensorimotor functions are executed (5). Viewed from a traditional experimental psychology perspective, processing speed can be conceived as the total sum of three different stages of information processing, namely perceptual analysis, response selection, and response execution (6, 7).

Although there are several neuropsychological tests for measuring reduced processing speed, a recent meta-analysis (8) has demonstrated that a digit–symbol-coding task is the most sensitive test to apply to patients with schizophrenia. Moreover, this meta-analysis identified processing speed impairment as the largest single deficit in the cognitive abilities of schizophrenia (8, 9).

Digit–symbol-coding tasks have been carried out in two different ways. In one version, the Digit–Symbol Substitution Test (DSST), symbols have to be drawn under their corresponding digits according to a key of digit–symbol combinations, provided at the top of the sheet. The second version is the symbol-coding subtest of the Brief Assessment of Cognition in Schizophrenia included in the MATRICS Final Battery (7, 10). This task does not require the drawing of symbols but rather the numerals (1–9) have to be written as quickly as possible under the corresponding symbols, which are presented in rows on the response sheet. This version of the coding task has been called the Symbol–Digit Substitution Test (SDST). In the present study, as in our previous studies (5, 11), we have used the SDST in order to avoid drawing unfamiliar graphic symbols, which requires a time consuming process of motor planning.

In the measurement of processing speed using a digit–symbol-coding task, at least two factors might play a considerable role. First, digit–symbol-coding tasks have a strong sensorimotor component (i.e., fine motor writing skills of the symbols or the digits). A reduction in sensorimotor speed, characterized by a longer initiation and/or execution of graphic movements, might indeed contribute substantially to low coding task performance. Previous research by Morrens et al. has demonstrated that schizophrenia patients display both sensorimotor and cognitive slowing and that these two processes are unrelated to each other (11).

In addition to a possible sensorimotor component, a second possible factor, which may influence the measurement of processing speed is het effect of (implicit) learning of the specific symbol–digit combinations. Learning is a well-known impairment in schizophrenia (9, 12–14) in addition to processing speed. Once the symbol–digit relationships are learned, it is no longer necessary to rely on visual scanning of the key on top of the administration sheet, rather working or episodic memory can be used instead for the right response. This strategy might reduce the time in finding the right response, resulting in an increased score on the test. There may be large individual differences in the speed of learning these symbol–digit relations and in their memory capacity. Similarly, Bachman et al. (15) and Joy et al. (16) proposed that a reduced cognitive processing speed in schizophrenia might be partially due to a mnemonic deficit. Other studies on this topic concluded that the contribution of memory to symbol–digit coding performance might be relatively small but relevant (16).

However, many of these previous studies have used regression-based approaches in which coding performance was correlated with additional neuropsychological tests (15). In an older version of the Wechsler Adult Intelligence Scale (WAIS-III), the Digit–Symbol-coding test was even followed by an implicit learning test to assess the recall of the symbol–digit relations (17). Bachman et al. rightly argued for a complementary experimental approach in which the symbol-coding task is manipulated to determine the role that several sub-processes might play in coding tasks. However, a disadvantage of this latter approach is that changing the task might have consequences for the relative contribution of these sub-processes.

In this experimental study, the subjects' pen movements were recorded on a writing tablet under the test sheet in order to precisely measure the time taken to write each digit (writing time) as well as the preceding time necessary to decode a symbol into its corresponding digit (matching time). The task requires to write the digits as quickly as possible; therefore, the writing time provides an estimate of sensorimotor speed whereas matching time reflects the duration of the cognitive processes that are needed to find or recall the digit that corresponds to the stimulus symbol.

Because matching time and writing time were registered for every single digit, the decrease per symbol–digit combination offers an estimate of both the rate and the amount of learning within one (90 s) test administration. In addition, by administering the same test on three separate days, we were able to assess the amount of long-term learning of the symbol–digit relations.

Schizophrenia has been previously hypothesized as a generalized syndrome of accelerated aging (18). Since the earliest descriptions by Emil Kraepelin, schizophrenia has been referred to as "dementia praecox," literally meaning "a cognitive decline in young age." A number of studies have shown that processing speed as measured by the SDST is a fundamental mediator of age-related cognitive decline (19, 20). Therefore, comparing the performance of schizophrenia patients to elderly individuals could offer secondary, but valuable information as to what extent and in which domains the cognitive decline in schizophrenia resembles age-related cognitive impairment, referred to as "mild cognitive impairment." To our knowledge, a direct comparison of performance on the SDST between schizophrenic and elderly individuals has never been conducted.

In summary, the present study was set up to investigate the relative contribution of learning and sensorimotor speed during SDST performance. Patients with schizophrenia, age-matched healthy controls, and elderly volunteers were tested in order to assess different effects of these factors in the different groups. The first hypothesis was that overall test performance would be lower in schizophrenia patients compared with age-matched healthy controls. In addition, it was expected that this study would replicate the well-known findings of reduced writing speed in schizophrenia. As visual and verbal learning and memory have been frequently found to be impaired in patients with schizophrenia (7), it was further hypothesized that the rate and amount of the learning of

the symbol–digit relations would be reduced in the schizophrenia patients. The comparison of schizophrenic and elderly individuals was exploratory.

MATERIALS AND METHODS

STUDY DESIGN

Our study group consisted of 30 patients with stable schizophrenia, 30 age- and sex-matched control participants, and 30 sex-matched elderly volunteers (aged 65–85 years). The SDST was administered three times on three separate assessment days. The test was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Clinical Practices, applicable regulatory requirements, and in compliance with the study protocol. This study was held at the University Psychiatric Hospital Duffel, Belgium, and the study protocol was reviewed and approved by the institute's Ethics Committee.

PARTICIPANTS

The previously mentioned test subjects were recruited from the local community. Prior to the start of the study, they all provided a written informed consent and their eligibility for this study was assessed according to some inclusion and exclusion criteria. The inclusion criteria for patients were: (1) being an in- or outpatient with schizophrenia or schizoaffective disorder (DSM-IV), (2) having a known history of schizophrenia for at least 12 months, confirmed by the treating psychiatrist, and (3) receiving stable antipsychotic drug therapy (maximally 2) for at least 6 weeks prior to screening. The inclusion criteria for all participants were: (1) being a man or woman between 18 and 55 years old (schizophrenia patients and young controls) or between 65 and 85 years old (elderly volunteers) and (2) being medically stable.

The exclusion criteria applicable to all participants were (1) having a DSM-IV diagnosis of substance dependence or abuse within 3 months prior to screening evaluation (only caffeine dependence was not exclusionary), (2) use of benzodiazepines, tricyclic antidepressants, or anticholinergic medication, (3) having a positive urine screen for drug abuse or a positive alcohol breath test at screening on one of the test days, (4) having a clinically significant acute illness within 7 days prior to screening. Since the use of alcohol and drugs could potentially influence the study data, an alcohol breath test and a urine drug screen were performed before the start of each assessment day.

SYMBOL–DIGIT SUBSTITUTION TEST

The task was performed on two subsequent sessions (day 1 and day 2) and a third time (day 7). The SDST was the first task to be performed on every assessment day in a larger series of cognitive tests, which will be published elsewhere. In order to avoid influences of the circadian rhythm, also the time on which the test was administered was comparable for each subject.

The coding task required to translate 9 different symbols into the digits 1–9 on five rows each consisting of 25 symbols, according to a key of symbol–digit pairs, which was presented on top of the task sheet. The same symbol–digit combinations were repeated over the three session days. In line with our previous studies (5, 11, 21), we used the reversed version of the classical DSST where the digits had to be written under the symbols, denoted by SDST. We chose for this design in order to exclude the complication of processes of motor planning by the drawing of complex graphic symbols on SDST performance. The nine different symbols were presented in blocks. The sequence in which they were presented within each block was randomized.

A quiet environment was chosen to perform this task. The participants were asked to decode the list of symbols one by one as fast as possible within a preset 90s limit, based on the key above, writing the correct digit under the corresponding symbol on a sheet of paper placed on a digitizing tablet (WACOM1218RE) with a special pressure-sensitive normal-looking ballpoint pen. Pen position was recorded at 200 Hz and with 0.2 mm spatial accuracy, and stored on a standard personal computer. The signals were subsequently filtered by means of a fast-Fourier analysis. These digitized recordings allowed the computation of separate matching- and writing times.

Identical instructions were repeated each day, before the start of the task. Feedback was not provided at the end of the session. All subjects had to undergo a practice trial on the first assessment day, consisting of filling in the last 10 symbol–digit pairs, allowing them to get familiar with the experiment.

STATISTICAL ANALYSIS

All data were analyzed using a general linear model (GLM) repeated measures in IBM®SPSS® Version 22. First, we analyzed the Session effect (long-term learning) with Group (three levels) as the between-subjects variable and Session (or days, with three levels) as the within-subjects variable. A second analysis used Block (five levels; short-term learning) and Session (three levels) as the within-subject variables and Group (three levels) as the between-subject variable. We performed separate analyses for (1) the number of correct digits, (2) the mean matching time per digit, and (3) the mean writing time per digit. Wilk's Lambda was used in the tests of the within-variable effects. A p-value of <0.05 was considered significant.

The number of blocks that could be analyzed depended on the lowest test score (number correct) obtained by the participants. Matching and writing time were analyzed over five blocks (i.e., number correct is 45 or higher). This score was gained in all three sessions by 25 patients with schizophrenia, 28 elderly volunteers, and 28 controls. Including more participants in the analysis would result in too many missing values in the fourth and fifth block whereas analyzing more than five blocks would result in an unrepresentative low number of participants. Per block, the median matching time and median writing time were calculated. Only correct digits were analyzed and the first digit of a row was eliminated from analysis because the transport distance to this location was more than 20 cm instead of the normal 0.8 cm. In session 3, the data of one patient were missing.

RESULTS

The main objective of the present study was to evaluate the role of learning processes during SDST performance. Firstly, demographics will be prescribed (see Demographics) followed by their general test scores on the SDST [see Test score (Number of correct digits)]. Matching time and writing time of test scores were separately calculated (see Long-Term Learning Matching and Writing Time and Short-Term Learning Matching and Writing Time Over Blocks

Per session), and the added effects of long-term learning (section Long-Term Learning Matching and Writing Time) and short-term learning (see Short-Term Learning Matching and Writing Time Over Blocks Per session) were assessed. In a final section (see Estimating the Effect of Short-Term Learning on the SDST Score), the relative contribution of short-term learning on the overall SDST score was calculated.

DEMOGRAPHICS

The demographic features of the three study groups are shown in **Table 1**. All patients used antipsychotic medication at the time of testing. Sixteen schizophrenia patients were using more than one antipsychotic drug. The distribution of the different antipsychotic drugs and range of daily doses are summarized elsewhere (22). Seven young controls, two schizophrenia patients, and no elderly individuals were left-handed. A GLM repeated measures analysis was conducted on the performance of the SDST (number correct) for the young control group with "Session" as within-subject variable and "Handedness" as between-subject variable. "Handedness" did not have a significant influence on the overall test score. The schizophrenia group had a lower mean IQ, as measured by the Adult Reading Test/ART (Dutch version: Nederlandse Leestekst voor Volwassenen/NLV), than the control group ($t = 3.96, p = 0.0002$) and the elderly group ($t = 4.71, p < 0.0001$).

Table 1 | Demographics.

		Schizophrenia	Elderly	Control
N		**30**	**30**	**30**
Age	Mean (SD)	36.43 (7.83)	69.33 (3.89)	36.77 (8.55)
	Range	23–53	65–79	18–52
IQ (ART)	Mean (SD)	101.3 (10.30)	111.7 (6.43)	110.1 (6.39)
	Range	66–115	100–124	98–130
Sex	male: female	2:1	2:1	2:1
Race	Asian	0	0	1
	Maghreb	1	0	0
	White	29	30	29

TEST SCORE (NUMBER OF CORRECT DIGITS)

The mean number of correct digits per session is displayed in **Figure 1** for each group. This figure clearly shows an increase in task performance (long-term learning effect) over the three sessions, which was significant [$F(2,85) = 36.21$, $p < 0.001$]. This learning effect was about equal in the three groups (Session*Group interaction $p = 0.119$).

On average, the three groups differed significantly in their overall score [$F(2,86) = 21.69$, $p < 0.001$]. Both schizophrenia patients and the elderly volunteers achieved a lower test score than the controls ($p < 0.001$). **Figure 1** gives the impression that the schizophrenia group performed even worse than the elderly, but the difference between these groups was not significant ($p = 0.07$) but

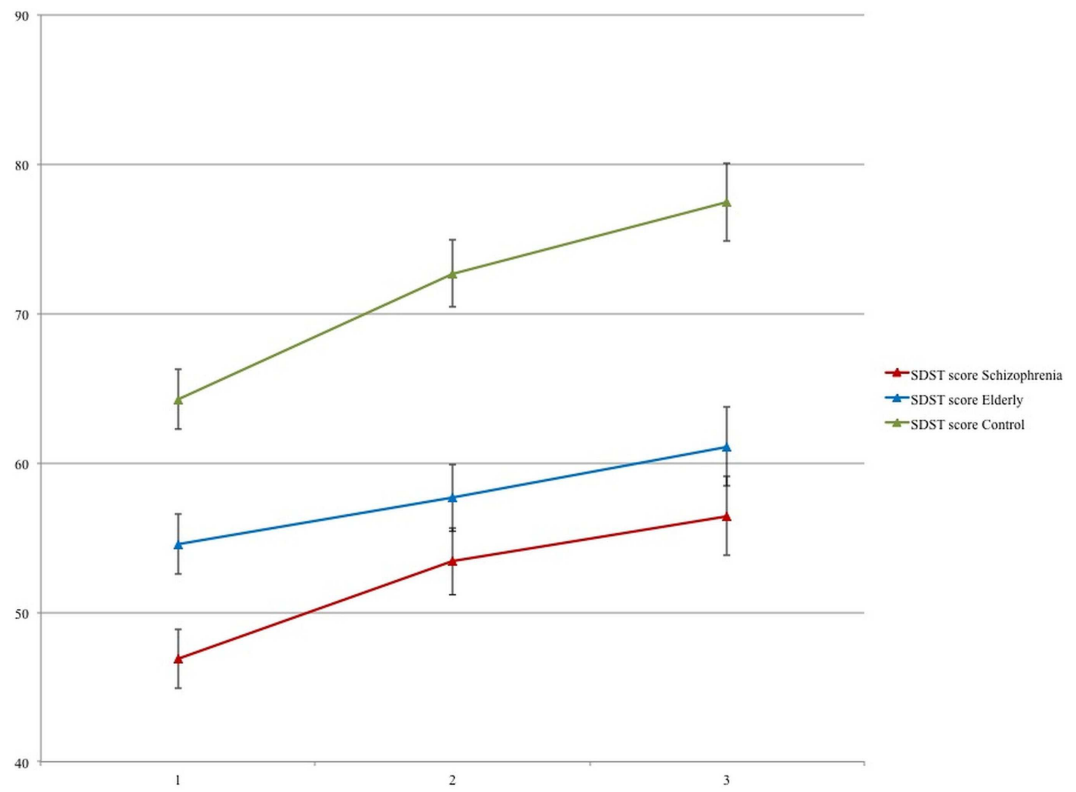


FIGURE 1 | Means and SE of the number of correct digits per session for schizophrenia patients, elderly volunteers, and young controls.

this was only true during the first session ($p = 0.028$). After incorporating IQ as a covariate in the analysis, the group difference between schizophrenia patients and controls remained significant [$F(1,56) = 23.61$, $p < 0.0001$], but the difference between schizophrenia and the elderly on session 1 was reduced to non-significance [$F(1,57) = 0.60$, $p = 0.443$].

LONG-TERM LEARNING MATCHING AND WRITING TIME

Mean matching time per digit and mean writing time per digit are presented in **Figure 2** for each session and each group.

Mean matching time per session

Figure 2 demonstrates that the matching times mirror the SDST performance of **Figure 1**. A clear learning effect over sessions was found [$F(2,85) = 32.46$, $p < 0.0001$], which was equal for the three groups [Group*Session interaction: $F(2,85) = 1.49$, $p = 0.206$]. Averaged over all sessions, the matching times in each group differed significantly from each other [$F(2,86) = 13.39$, $p < 0.001$]. Planned contrasts show a significant difference between patients and controls ($p < 0.0001$), between patients and elderly ($p = 0.002$ after Bonferroni correction), but not between the elderly and the controls ($p = 0.167$). IQ (ART) as a covariate was significant [$F(1,85) = 14.50$, $p = 0.0003$]. IQ did not influence the difference between patients and controls ($p = 0.001$) but reduced the difference between elderly and schizophrenic participants to non-significance ($p = 0.282$).

Mean writing time per session

The writing times as displayed in **Figure 2** do not show much variation over the test sessions, and the session effect was not significant [$F(2,85) = 1.36$, $p = 0.262$]. Therefore, we may conclude that there was no evident learning in the writing of the digits. Neither was the Group*Session interaction significant [$F(4,170) = 0.45$, $p = 0.771$]. On the other hand, the differences between the groups were relatively large and significant [$F(2,86) = 26.37$, $p < 0.0001$]. The elderly wrote significantly slower than the patients ($p = 0.0003$) and the patients wrote significantly slower than the controls ($p = 0.001$).

SHORT-TERM LEARNING MATCHING AND WRITING TIME OVER BLOCKS PER SESSION

Within-session learning effects are shown in **Figure 3**, which displays mean matching and writing times per digit for each of the five blocks in the three sessions.

Mean matching time per block

Figure 3 illustrates a decrease in matching time over the blocks and over sessions. A GLM repeated measures analysis confirmed that matching time decreased significantly over blocks [short-term learning; $F(4,75) = 21.66$, $p < 0.0001$] and over sessions [long-term learning; $F(4,75) = 21.66$, $p < 0.0001$]. The decrease over blocks was about equal in the three sessions [$F(8,71) = 1.74$, $p = 0.105$] and seemed to be similar in the three groups [$F(8,150) = 1.709$, $p = 0.101$], but the highest order interaction (session*block*group) was significant [$F(16,142) = 1.79$, $p = 0.038$]. Therefore, separate analyses were run per session. In these analyses, only the linear block effect was tested (i.e., a linear decrement of matching time over blocks; see the dashed lines in **Figure 3**). In session 1, this linear block effect was significant [$F(1,78) = 31.04$, $p < 0.0001$], denoting a significant short-term learning effect (decrement over blocks), but this learning effect was similar for the three groups [block*group Linear: $F(2,78) = 0.03$, $p = 0.597$]. In the second and third sessions, more participants reached the minimum criterion of 45

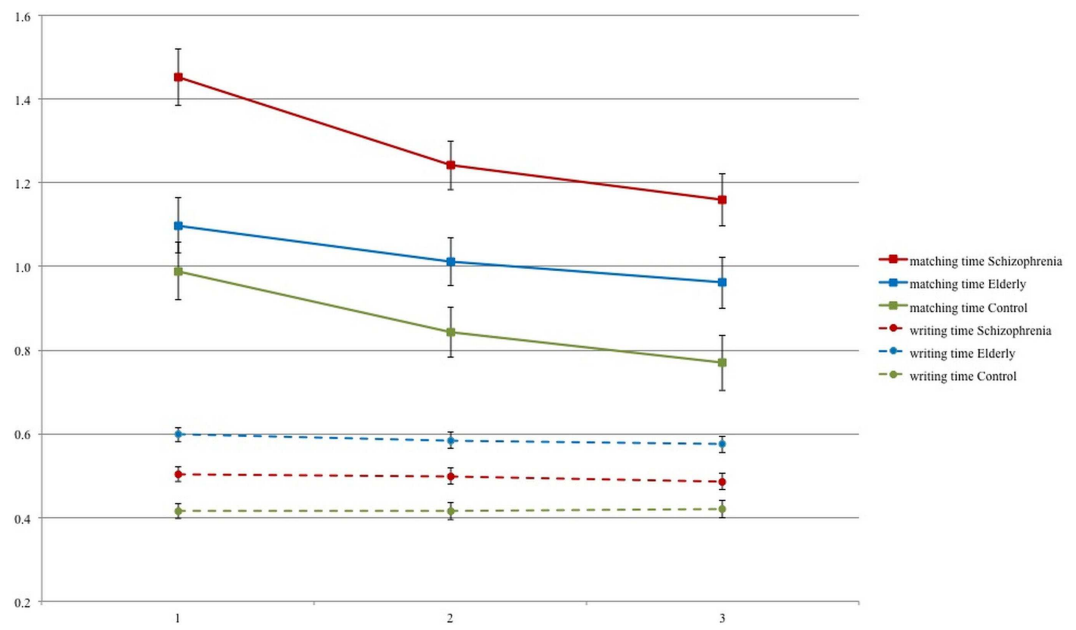


FIGURE 2 | Means and SE for matching and writing time per session for schizophrenia patients, elderly volunteers, and young controls.

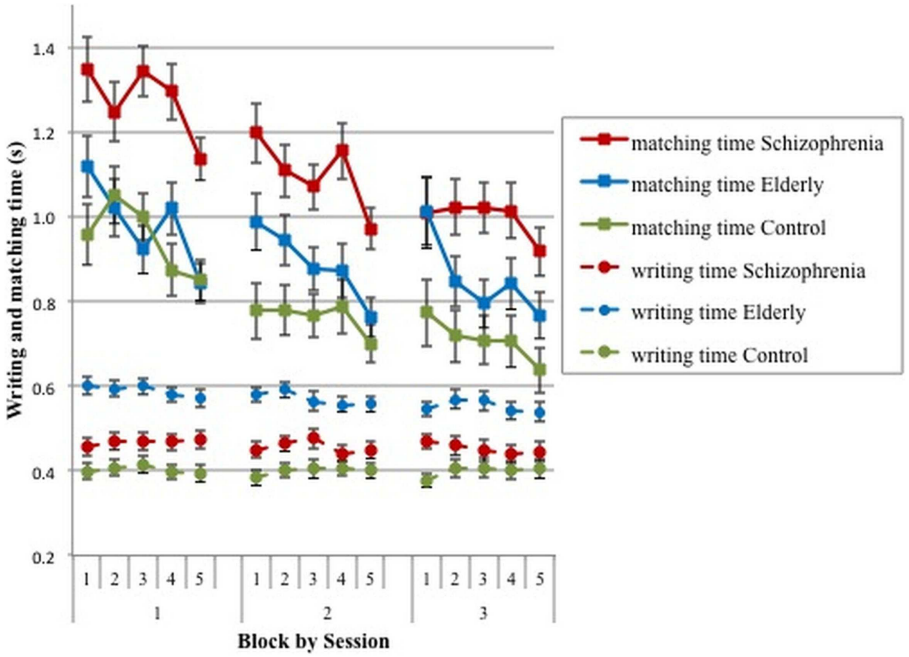


FIGURE 3 | Means and SE for writing and matching time per block and per session for schizophrenia patients, elderly volunteers, and young controls.

correct digits, but the analyses of the Linear trends yielded similar results [session 2: block: $F(1,83) = 29.08$, $p < 0.0001$; block*group Linear: $F(2,83) = 2.75$, $p = 0.070$; session 3: block: $F(1,83) = 25.20$, $p < 0.0001$; block*group Linear: $F(2,83) = 1.95$, $p = 0.148$]. Therefore, these results suggest that the rate and amount of short-term learning (repetition over blocks) was similar in the three sessions and about equal among the three groups.

Mean writing time per block

Writing time in **Figure 3** shows that there is not much variation over blocks and sessions. The only noteworthy result is the relatively long writing time of the elderly participants.

An analysis of writing time with session and block as the within-subject variables and group as the between-subject variable showed that the effect of session was not significant but the block effect was [$F(4,75) = 5.60$, $p = 0.0003$]. None of the interactions were significant either. In the first session, the linear block effect was not significant ($p = 0.216$), but the linear block*group interaction was significant [$F(2,78) = 3.55$, $p = 0.033$]. This is probably due to a slight decrement of writing time by the elderly but not by the other two groups. In the second and third session, the linear block effect and the linear block*group interactions were not significant, indicating that writing time remained stable in these sessions.

ESTIMATING THE EFFECT OF SHORT-TERM LEARNING ON THE SDST SCORE

To estimate the contribution of the linear decrease in matching time to the SDST score, we estimated the score that would have been obtained if the matching time (mt) and writing time (wt) of the first block (i.e., mt1 and wt1) had been maintained over all blocks in the 90 s of the test [i.e., estimated score = 90/(mt1 + wt1)]. We did the same for block five. The result of this estimation for session 1, i.e., for the standard test administration, was that the score of all participants had improved, more specifically from 50 to 56 for patients with schizophrenia, from 52 to 64 for the elderly and from 66 to 72 for the controls. These are increases of 12, 23, and 9%, respectively. It should, however, be stipulated that not all participants showed a decrease in matching time over blocks. Slopes ranged considerably, with the largest range found in the group of schizophrenia patients (from +78 ms/block to −301 ms/block; mean = −37 ms/block) compared to the ranges of the young controls (from + 50 ms/block to −284 ms/block; mean = −39 ms/block) and the elderly volunteers (from + 38 ms/block to −236 ms/block; mean = −55 ms/block).

DISCUSSION

SUMMARY OF RESULTS

The main purpose of this study was to assess to what extent differences in symbol–digit learning influence the performance on the SDST. The present findings demonstrate that the repetition of symbol–digit pairs during one test administration (short-term learning), and the repetition of the same test over several days (long-term learning), resulted in significant decreases of matching time. Interestingly, these learning effects on matching time were about equal for patients, age-matched controls, and elderly participants, while the overall test score differed among the groups. In contrast, writing time, reflecting sensorimotor speed, remained about equal over symbol–digit repetitions. Patients had the lowest overall score and the longest matching time; however, the difference between patients with schizophrenia and elderly was no longer significant after controlling for the lower IQ of the patients.

Sensorimotor speed had a smaller impact on the overall test performance, but there were significant differences between the three groups with the elderly clearly being the slowest writers.

RATIONALE FOR THE CHOSEN METHODOLOGICAL APPROACH

In an experimental approach of the coding task, like the one adopted by Bachman et al. (15), single symbol–digit pairs are presented trial by trial and on each trial the participant has to quickly decide whether the presented combination is identical to one of the digit–symbol pairs in the reference code that is simultaneously presented on the PC screen. In the more common paper-and-pencil version of the task, the participant can work at his own pace and might (learn to) combine the activities of both writing a digit and searching for the next digit that matches the next symbol in parallel. We opted to incorporate an experimental approach into the continuous paper-and-pencil version, because recording of the pen movements enables the separate measurement of reaction time (now denoted by "matching" time) and response execution time ("writing" time).

In addition, to allow an unbiased estimate of learning we adapted the presentation of the symbols that had to be coded. In standard symbol-coding tests, not all nine symbols are already shown in the first block but they are introduced gradually to promote the learning of the symbol–digit relations. For our SDST version, however, we preferred to present all nine symbols with the same frequency right from the start. As a result, a repetition of the same symbol–digit pair was separated by an average of eight other pairs. Yet, considerable learning did occur as evidenced by the linear decrease in matching time over nine-symbol blocks.

INFLUENCE OF LEARNING PROCESSES ON THE SDST TEST SCORE

Comparing the size of the learning effects with the SDST scores showed that the influence of learning processes on the SDST score in schizophrenia, the elderly and younger controls varies greatly from person to person. The average learning effects found in the present study of about 12% in the schizophrenia group and 23% in the elderly can be classified as rather substantial. This is in line with the conclusions drawn by Bachman et al. (15) and Joy (16). It deviates from Salthouse's (23) interpretation in which memory factors are assigned only "a very small role in contributing to the age decline in digit–symbol performance."

IDENTIFICATION OF LEARNING PROCESSES

Repetition of the same task results in learning. Therefore, the decrease in matching time over blocks within one session as well as over more sessions must be the result of a learning process. But what exactly is learned during the repetitions of symbol–digit pairs is less clear. Two critical processes are known to be involved in the search for the matching digit: visual scanning (24) and relational memory (16). First, visual scanning, refers to the early detection and identification of visual stimuli, either alone or in the presence of competing stimuli. The role of visual scanning is emphasized when participants consult the code key frequently during test administration. Possibly, visual scanning might improve by learning the position of the symbols in the key. Second, relational memory, refers in this context to the memory for associations in the SDST (10, 12). Learning the relations between symbols and digits will reduce the necessity for searching, which automatically results in a decreased matching time. A third process that might be involved in the reduction of matching time over repetitions is a change in the strategy to perform the task. An impairment in response selection (25, 26), i.e., the process of mapping stimuli to specific responses and decision making could possibly cause a considerable amount of the lower performance observed in schizophrenia. Most participants will start with performing matching and writing strictly after each other, while some participants might learn to do part of the writing and scanning in parallel. In that case, the search for the next digit has already started during the more or less automatic writing of the current number. Overall, various learning processes might contribute to a decreased matching time, but their relative contribution could not be deduced from the present study. To find more detailed answers, experimental changes of the task, like the manipulations tested by Bachman et al., are needed. For now, we can only conclude that these learning processes occurred unintentionally, and therefore, should be denoted by the term "implicit learning." An important outcome of this study is that the rate of this implicit learning was not significantly different among the three groups.

SENSORIMOTOR SPEED

The second aim of our investigation was to evaluate the effect of differences in writing speed on the SDST score. Group differences in writing speed were highly significant but smaller than the group differences in matching time. Schizophrenia patients wrote significantly slower than same-aged controls and the elderly had the lowest writing speed. The effects of reduced writing speed in schizophrenia and the elderly on the total test score were smaller than the estimated effects of learning (for schizophrenia, learning + 12%, writing speed + 4%; for the elderly, learning + 23%, writing speed + 13%). This leads us to the conclusion that the usual determination of the symbol-coding test score results in underestimation of the speed of information processing, particularly for the elderly.

SCHIZOPHRENIA AND THE ELDERLY COMPARED

Healthy elderly persons were included in this study in order to compare the reduction in the speed of information processing of the schizophrenia patients with normal, age-related cognitive decline. By correcting for sensorimotor speed and only taking the matching time as an index of processing speed, patients performed worse compared to the elderly volunteers (aged 65–85 years). However, when an estimate of premorbid intelligence (the Adult Reading Test) was taken into account, the differences in matching time were no longer statistically significant, while the difference between patients and same-aged controls still remained significant. Although the similarity between the elderly and the patients with schizophrenia on matching time is striking, we cannot deduce from these data whether schizophrenia should be seen as "dementia praecox." In addition, it should be acknowledged that the elderly had a small but significantly lower sensorimotor speed. Only sensorimotor speed differentiated all three groups.

STUDY LIMITATIONS

Due to patient selection, a bias might exist since only patients who were able to complete the test batteries were included in this study.

The neurocognitive abilities of the selected patients may therefore be higher than the group of schizophrenia at large. Thus, the results of this study may not be generalized to the whole population of patients with schizophrenia. However, the mean SANS score for schizophrenia patients of 25.7 (SD 17.39) that was measured on screening visit is comparable with the mean SANS score of 23.0 (SD 14.6) found in a large heterogeneous sample of schizophrenia patients (27). Additionally, only 4.2% of our study sample was excluded after screening visit, suggesting that the internal validity of our study is high.

IMPLICATIONS FOR FUTURE RESEARCH AND CLINICAL PRACTICE

There is a wide variation in the administration of symbol–digit coding tasks ranging from a classical pen-and-paper writing task to a purely computerized test, which simply requires pressing a button when the correct symbol–digit combination appears. These different methods may ask for different cognitive sub-processes in the total test score. As an example of this, the present study clearly showed that the time taken by the motor part of the test must be taken into account in interpreting symbol–digit coding test scores as measures of the speed of information processing. The large variation between individual participants in the rate of short-term learning could argue for the need of additional memory test information to assess to what extent the (possibly) low SDST score has been the result of a learning failure. Some healthy volunteers mentioned spontaneously at the end of a session that they had remembered the symbol–digit combinations but we did not give a questionnaire to draw further conclusions toward awareness differences among the groups. Therefore, we suggest that the addition of a self-rater or observer-rater questionnaire might be valuable to address the possibility of different explicit and implicit learning strategies.

Although schizophrenia is often characterized by a reduced speed of information processing, the present study showed a similarity with the control group and the elderly as far as the rate and amount of both short-term and long-term implicit learning was involved. This was found despite the general finding of impaired working memory and a lower rate of explicit verbal and visual learning in schizophrenia. Because we speculate that improving processing speed may be predictive for the functional outcome, we recommend that more attention should be paid to implicit learning in future schizophrenia research and in the design of specific rehabilitation programs.

CONCLUSION

We can conclude that the two factors that were studied both had an effect on the estimation of processing speed with the Symbol–Digit Substitution Test. The average effect of learning the symbol–digit relation on the SDST score was substantial and the large individual differences in the amount of learning deserves more attention. The effects of sensorimotor speed on the total test score were shown to be smaller than the learning effects, but cannot be neglected because they lead to an underestimation of the speed of information processing, particularly for the elderly.

The finding of equal unintentional learning effects in patients, their age-matched controls and elderly participants lead us to the conclusion that implicit learning might be preserved in schizophrenia. This finding has important consequences for the design of specific rehabilitation programs for schizophrenia patients.

AUTHOR CONTRIBUTIONS

All authors met ICMJE criteria and all those who fulfilled those criteria were listed as authors. All authors had access to the study data and made the final decision about where to present these data.

ACKNOWLEDGMENTS

The authors would like to thank Dr. Fransen (StatUA) for additional statistical guidance, Ms. Morsel for her guidance and refinement of the English writing style and Ms. Apers, Ms. Laureys and Ms. Vermeylen for their support in the testing of the study participants. The authors also thank the study participants, without whom the study would never have been accomplished.

REFERENCES

1. Weinberger DR, Gallhofer B. Cognitive function in schizophrenia. *Int Clin Psychopharmacol* (1997) **4**:29–36. doi:10.1097/00004850-199709004-00006
2. Nuechterlein KH, Ventura J, Subotnik KL, Bartzokis G. The early longitudinal course of cognitive deficits in schizophrenia. *J Clin Psychiatry* (2014) **75**:25–9. doi:10.4088/JCP.13065.su1.06
3. Nuechterlein KH, Barch DM, Gold JM, Goldberg TE, Green MF, Heaton RK. Identification of separable cognitive factors in schizophrenia. *Schizophr Res* (2004) **72**:29–39. doi:10.1016/j.schres.2004.09.007
4. Brébion G, Amador X, Smith MJ, Gorman JM. Memory impairment and schizophrenia: the role of processing speed. *Schizophr Res* (1998) **30**:31–9. doi:10.1016/S0920-9964(97)00123-0
5. Morrens M, Hulstijn W, Matton C, Madani Y, van BouwelL, Peuskens J, et al. Delineating psychomotor slowing from reduced processing speed in schizophrenia. *Cogn Neuropsychiatry* (2008) **13**:457–71. doi:10.1080/13546800802439312
6. Pashler H. Dual-task interference in simple tasks: data and theory. *Psychol Bull* (1994) **116**:220–44. doi:10.1037/0033-2909.116.2.220
7. Nuechterlein KH, Green MF, Kern RS, Baade LE, Barch DM, Cohen JD, et al. The MATRICS consensus cognitive battery, part 1: test selection, reliability, and validity. *Am J Psychiatry* (2008) **165**:203–13. doi:10.1176/appi.ajp.2007.07010042
8. Dickinson D, Ramsey ME, Gold JM. Overlooking the obvious: a meta-analytic comparison of digit symbol coding tasks and other cognitive measures in schizophrenia. *Arch Gen Psychiatry* (2007) **64**:532–42. doi:10.1001/archpsyc.64.5.532
9. Knowles EEM, David AS, Reichenberg A. Processing speed deficits in schizophrenia: reexamining the evidence. *Am J Psychiatry* (2010) **167**:828–35. doi:10.1176/appi.ajp.2010.09070937
10. Green MF, Nuechterlein KH, Gold JM, Barch DM, Cohen J, Essock S, et al. Approaching a consensus cognitive battery for clinical trials in schizophrenia: the NIMH-MATRICS conference to select cognitive domains and test criteria. *Biol Psychiatry* (2004) **56**:301–7. doi:10.1016/j.biopsych.2004.06.023
11. Morrens M, Hulstijn W, Van Hecke J, Peuskens J, Sabbe BGC. Sensorimotor and cognitive slowing in schizophrenia as measured by the symbol digit substitution test. *J Psychiatr Res* (2006) **40**:200–6. doi:10.1016/j.jpsychires.2005.04.014
12. Horan WP, Green MF, Knowlton BJ, Wynn JK, Mintz J, Nuechterlein KH. Impaired implicit learning in schizophrenia. *Neuropsychology* (2008) **22**:606–17. doi:10.1037/a0012602
13. McDowd J, Tang T-C, Tsai P-C, Wang S-Y, Su C-Y. The association between verbal memory, processing speed, negative symptoms and functional capacity in schizophrenia. *Psychiatry Res* (2011) **187**:329–34. doi:10.1016/j.psychres.2011.01.017
14. Morrens M, Hulstijn W, Sabbe B. Psychomotor slowing in schizophrenia. *Schizophr Bull* (2007) **33**:1038–53. doi:10.1093/schbul/sbl051
15. Bachman P, Reichenberg A, Rice P, Woolsey M, Chaves O, Martinez D, et al. Deconstructing processing speed deficits in schizophrenia: application of a parametric digit symbol coding test. *Schizophr Res* (2010) **118**:6–11. doi:10.1016/j.schres.2010.02.1029
16. Joy S, Fein D, Kaplan E. Decoding digit symbol: speed, memory, and visual scanning. *Assessment* (2003) **10**:56–65. doi:10.1177/0095399702250335

17. Lezak MD, Howieson DB, Loring DW. *Neuropsychological Assessment. Fourth Edition*. New York: Oxford University Press (2004).
18. Kirkpatrick B, Messias E, Harvey PD, Fernandez-Egea E, Bowie CR. Is schizophrenia a syndrome of accelerated aging? *Schizophr Bull* (2008) **34**:1024–32. doi:10.1093/schbul/sbm140
19. Crawford JR, Bryan J, Luszcz MA. The executive decline hypothesis of cognitive aging: do executive deficits qualify as differential deficits and do they mediate age-related memory decline? *Aging Neuropsychol Cogn* (2000) **7**:9–31. doi:10.1076/anec.7.1.9.806
20. Baudouin A, Clarys D, Vanneste S, Isingrini M. Executive functioning and processing speed in age-related differences in memory: contribution of a coding task. *Brain Cogn* (2009) **71**:240–5. doi:10.1016/j.bandc.2009.08.007
21. Morrens M, Hulstijn W, Sabbe B. The effects of atypical and conventional antipsychotics on reduced processing speed and psychomotor slowing in schizophrenia: a cross-sectional exploratory study. *Clin Ther* (2008) **30**:684–92. doi:10.1016/j.clinthera.2008.04.012
22. De Picker L, Cornelis C, Hulstijn W, Dumont G, Fransen E, Morrens M. Preserved sensorimotor learning in stable schizophrenia patients but not in elderly participants compared to young controls in two variations of the Rotary Pursuit. *Front Psychiatry* (2014) **5**:165. doi:10.3389/fpsyt.2014.00165
23. Salthouse TA. The role of memory in the age decline in digit-symbol substitution performance. *J Gerontol* (1978) **33**:232–8. doi:10.1093/geronj/33.2.232
24. Mahurin RK, Velligan DI, Miller AL. Executive-frontal lobe cognitive dysfunction in schizophrenia: a symptom subtype analysis. *Psychiatry Res* (1998) **79**:139–49. doi:10.1016/S0165-1781(98)00031-6
25. Woodward ND, Duffy B, Karbasforoushan H. Prefrontal cortex activity during response selection predicts processing speed impairment in schizophrenia. *J Int Neuropsychol Soc* (2013) **19**:782–91. doi:10.1017/S1355617713000532
26. Krieger S, Lis S, Janik H, Cetin T, Gallhofer B, Meyer-Lindenberg A. Executive function and cognitive subprocesses in first-episode, drug-naive schizophrenia: an analysis of N-back performance. *Am J Psychiatry* (2005) **162**:1206–8. doi:10.1176/appi.ajp.162.6.1206
27. van Erp TG, Preda A, Nguyen D, Faziola L, Turner J, Bustillo J, et al. Converting positive and negative symptom scores between PANSS and SAPS/SANS. *Schizophr Res* (2014) **152**:289–94. doi:10.1016/j.schres.2013.11.013

Conflict of Interest Statement: This study was funded by Janssen Research and Development, a division of Janssen Pharmaceutica N.V. Mr. Janssens and Mr. Timmers are employees of Janssen Research and Development, a division of Janssen Pharmaceutica N.V., Beerse, Belgium, and own stock/stock options in the company.

Received: 30 September 2014; accepted: 12 December 2014; published online: 06 January 2015.
*Citation: Cornelis C, De Picker LJ, Hulstijn W, Dumont G, Timmers M, Janssens L, Sabbe BGC and Morrens M (2015) Preserved learning during the symbol–digit substitution test in patients with schizophrenia, age-matched controls, and elderly. Front. Psychiatry **5**:189. doi: 10.3389/fpsyt.2014.00189*
This article was submitted to Schizophrenia, a section of the journal Frontiers in Psychiatry.

frontiers in PSYCHIATRY

ORIGINAL RESEARCH ARTICLE
published: 24 November 2014
doi: 10.3389/fpsyt.2014.00165

Stable schizophrenia patients learn equally well as age-matched controls and better than elderly controls in two sensorimotor rotary pursuit tasks

Livia J. De Picker[1,2]*, Claudia Cornelis[1,2], Wouter Hulstijn[1,3], Glenn Dumont[1,2], Erik Fransen[4], Maarten Timmers[5], Luc Janssens[5], Manuel Morrens[1] and Bernard G. C. Sabbe[1,2]

[1] *Collaborative Antwerp Psychiatric Research Initiative (CAPRI), University of Antwerp, Antwerp, Belgium*
[2] *University Psychiatric Hospital St. Norbertushuis, Duffel, Belgium*
[3] *Donders Institute for Brain, Cognition and Behaviour, Radboud University Nijmegen, Nijmegen, The Netherlands*
[4] *StatUA, University of Antwerp, Antwerp, Belgium*
[5] *Janssen Research and Development, Janssen Pharmaceutica N.V., Beerse, Belgium*

Edited by:
Sebastian Walther, University Hospital of Psychiatry, Switzerland

Reviewed by:
Dusan Hirjak, University of Heidelberg, Germany
Valentin Johannes Benzing, University Hospital of Psychiatry, Switzerland

****Correspondence:***
Livia J. De Picker, Collaborative Antwerp Psychiatric Research Institute (CAPRI), University of Antwerp, Campus Drie Eiken R.321, Universiteitsplein 1, 2610 Wilrijk, Belgium
e-mail: livia.depicker@uantwerp.be

Objective: To compare sensorimotor performance and learning in stable schizophrenia patients, healthy age- and sex-matched controls and elderly controls on two variations of the rotary pursuit: circle pursuit (true motor learning) and figure pursuit (motor and sequence learning).

Method: In the circle pursuit, a target circle, rotating with increasing speed along a predictable circular path on the computer screen, must be followed by a cursor controlled by a pen on a writing tablet. In the eight-trial figure pursuit, subjects learn to draw a complex figure by pursuing the target circle that moves along an invisible trajectory between and around several goals. Tasks were administered thrice (day 1, day 2, day 7) to 30 patients with stable schizophrenia (S), 30 healthy age- and sex-matched controls (C), and 30 elderly participants (>65 years; E) and recorded with a digitizing tablet and pressure-sensitive pen. The outcome measure accuracy (% of time that cursor is within the target) was used to assess performance.

Results: We observed significant group differences in accuracy, both in circle and figure pursuit tasks ($E < S < C$, $p < 0.01$). Strong learning effects were found in each group. Learning curves were similar in circle pursuit but differed between groups in figure pursuit. When corrected for group differences in starting level, the learning gains over the three sessions of schizophrenia patients and age-matched controls were equal and both were larger than those of the elderly controls.

Conclusion: Despite the reduced sensorimotor performance that was found in the schizophrenia patients, their sensorimotor learning seems to be preserved. The relevance of this finding for the evaluation of procedural learning in schizophrenia is discussed. The better performance and learning rate of the patients compared to the elderly controls was unexpected and deserves further study.

Keywords: rotor pursuit, schizophrenia, motor skills, learning curve, aging and cognitive function, procedural learning, motor learning

INTRODUCTION

The functional outcome of schizophrenia patients is highly impacted by the severity of their cognitive symptoms and their capacity to learn new skills (1). Two variants of learning are generally distinguished: declarative and procedural learning, the latter referring to skill, habit, or knowledge acquisition that occurs in an implicit manner, i.e., automatically and outside of conscious awareness (2). Sensorimotor learning, the incremental spatial and temporal accuracy of movements with repetition, represents a form of procedural learning involving different corticostriatal circuits from those in other forms, such as probabilistic classification (3).

Designed as a tool to evaluate motor learning, the rotor pursuit task has been first used in 1947 (4). It measures the ability to keep a stylus on a rotating target, requiring motor control over the proximal upper limb (including shoulder–elbow control and postural control), as well as the ability to continuously process and adapt to sensory (visual and proprioceptive) feedback. Rotor pursuit

Abbreviations: CPR, circle pursuit rotor; E group, elderly participants; FPR, figure pursuit rotor; GLM, general linear model; LCT, line-copying task; MT, movement time; NLV, *Nederlandse Leestest voor Volwassenen;* PR, pursuit rotor/rotary pursuit; RPM, rotations per minute; S group, schizophrenia patients; WCST, Wisconsin card sorting test; Y group, young controls.

performance is known to be altered in several pathologies involving the basal ganglia; impaired performance has been demonstrated in Huntington's and Parkinson's disease and enhanced performance in the early trials of the task is seen in patients with obsessive–compulsive disorder (5). The key substrate of the basal ganglia's involvement in sensorimotor performance and learning is represented by their extensive reciprocal connections to motor and premotor areas of the frontal lobe, implicated in planning and execution of movements (6). Besides the role of the striatal–cortical circuitry, which is considered particularly important in learning operated through the implicit mode, tracts involving the (pre)motor cortex, the supplementary motor area, and the cerebellum are also implicated in the generation of precise forces and spatial knowledge required for learning new motor skills (7).

In contrast to declarative tasks, in which schizophrenia patients have consistently shown impaired performance and learning compared to healthy controls, procedural learning has been less well studied. Both corticofrontal and striatal involvement are presumed in the pathophysiology of schizophrenia, and abnormal dopamine regulation within the basal ganglia is thought to contribute to the psychotic symptoms of the disease. However, studies examining patients with schizophrenia on the pursuit rotor motor-skill learning task have so far produced mixed results when comparing both general performance and learning rate of patients to healthy controls (see **Table 1**) (8–15). Reasons for the conflicting results may reflect methodological differences including in instrumentation, in equating for initial performance, in number of trials administered, or influences of intrinsic moderating variables, such as

Table 1 | Summary of sensorimotor skill studies with Pursuit rotor task in schizophrenia patients.

Author (year)	Huston and Shakow (1949)[8]	Goldberg et al. (1993)[9]	Granholm et al. (1993)[10]	Clare et al. (1993)[11]	Schwartz et al. (1996)[12]	Kern et al. (1997)[13]	Weickert et al. (2002)[14]	Gomar et al. (2011)[15]
Version	Contact	Contact	Photoelectric	Not specified	Contact	Photoelectric	Not specified	Digital
Design	2 blocks × 5 trials × 10 s	3 blocks × 5 trials × 20 s	6 blocks × 4 trials × 20 s	5 blocks × 6 trials × 20 s	6 blocks × 4 trials × 20 s	6 blocks × 4 trials × 20 s	6 blocks	6 blocks × 4 trials × 20 s
Days	d1	d1	d1	d1–d8	d1	d1	d1	d1–d8
N	SZ 122, C 60	24 discordant and 7 normal MZ twin pairs	SZ 11, C 11	SZ 11, C 12	SZ 40, C 40 (each 20 elderly, 20 young)	SZ 18, C 15	SZ 35, C 35	SZ 43, C 22
SZ age; mean (range)		31 (17–44)	38.4	42.7 (21–70)	YSZ 33.1 (26–40), ESZ 63.2 (55–70)	36.7	Not specified	46.9 (24–64)
SZ sex M:F		14:10	11:0	7:5	38:2	18:0	Not specified	34:9
RPM	60	30 and 60	45	30	ESZ 40.50, EC 48.75, YSZ 47.25, YC 56.25	SZ 37.2, C 62.7	Not specified	Not specified
Trial 1 matched?	No	No	No	No	Yes	Yes	Not specified	Yes
IQ matched?	No	No	No	No	No	No	Yes (subsample $n = 14$)	Yes (subsample $n = 22$)
Absolute performance difference	SZ < C	SZ = C	SZ = C	SZ < C	SZ < C	SZ = C	SZ < C; IQ matched SZ = C	SZ < C; IQ matched SZ = C
Learning rate difference	Not specified	Not specified	SZ = C	SZ = C	SZ < C	SZ = C	SZ = C	SZ = C

SZ, schizophrenia patients; C, controls; ESZ, elderly schizophrenia patients; EC, elderly controls; YSZ, young schizophrenia patients; YC, young controls; RPM, rotations per minute.

general intellectual capacity and declarative memory, as well as the effect of psychotropic drugs. It is also debated whether any impaired performance on the rotor pursuit may be related more to underlying psychomotor deficits or to general cognitive decline, both features of schizophrenia (16).

Considering the outcomes of previous studies using the rotor pursuit task in schizophrenia, we hypothesized that true sensorimotor learning would be preserved in schizophrenia patients (10, 11, 13–15). However, many tasks that measure procedural learning also include a cognitive aspect, e.g., in the form of an implicit sequence to be learned. It has been postulated that motor and cognitive aspects of procedural tasks are governed by different brain processes; motor or skill learning aspects have been associated with a corticostriatal motor circuit involving the putamen, whereas aspects of cognitive or habit learning are suggested to operate the dorsolateral prefrontal cortex circuit involving the caudate (14). Previous studies that have tried to compare performance on these two aspects have been using combinations of methodologically distinct tasks (e.g., rotor pursuit and a probabilistic classification task, such as the weather prediction task), complicating the direct comparison of their relative outcomes (14).

In this study, we aim to assess the cognitive and motor aspects involved in sensorimotor skill learning in the same pursuit task set up, by using two separate task variations, one of which incorporates also a sequence component.

Furthermore, a longitudinal set up with repeated sessions over several days offers the added value of distinguishing between early (encoding and acquisition) and late (retention/consolidation) phases of sensorimotor learning, as distinguished in literature (7).

An age-related decline in sensorimotor performance and learning on the rotor pursuit has been described (17). Besides the schizophrenia patients and age-matched controls, we, therefore, also included a group of elderly healthy participants to investigate whether the sensorimotor deficits in schizophrenia patients are comparable to those associated with advanced age. We expected both schizophrenia subjects and elderly participants to perform poorer than young control subjects in the sensorimotor rotary pursuit tasks.

MATERIALS AND METHODS

STUDY DESIGN

For all subjects enrolled, the study consisted of an eligibility screening examination (up to 21 days prior) and three cognitive assessment days. The screening examination included baseline assessments of executive functioning (Wisconsin Card Sorting Test; WCST), premorbid IQ (Dutch Adult Reading Test/*Nederlandse Leestest voor Volwassenen*; NLV), and psychomotor speed (measured with a line-copying task on a digitizing tablet; LCT).

Cognitive assessments were made in two subsequent sessions (days 1 and 2), which were separated by overnight sleep. An additional third session was performed on day 7. The pursuit task was part of a cognitive test battery of approximately 90 min that was administered to all subjects in the same way and will be reported elsewhere. The time of day for completion of the cognitive test batteries was comparable on all test days for each subject, but not identical for all subjects.

The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Clinical Practices, applicable regulatory requirements, and in compliance with the study protocol. The study protocol was reviewed and approved by the Institutional Ethics Committee.

PARTICIPANTS

After giving written informed consent, subjects were screened to ascertain their eligibility for the study according to the in- and exclusion criteria specific for the population enrolled. The patient sample consisted of 30 outpatients aged 18–55 with a known history of schizophrenia or schizo-affective disorder (based on DSM-IV criteria) of at least 12 months, as confirmed by the referring psychiatrist. Exclusion criteria were current use of drugs with anticholinergic properties (including tricyclic antidepressants) and benzodiazepines, or comorbid DSM-IV diagnosis of substance dependence within 3 months prior to screening evaluation (except for caffeine and nicotine dependence); patients with a positive drug screen at screening could be included provided they did not meet DSM-IV diagnosis of substance dependence and consented to abstain from illegal drugs at any time during the study. An alcohol breath test and urine drug screening were performed at each of the cognitive assay days. All patients were stably treated with antipsychotic medication for at least 6 weeks, with no more than two different antipsychotic drugs used concurrently. Patients were judged to be in stable clinical condition at the time of testing through subject interview and medical history review by a trained clinician. Symptom severity of patients was rated at screening by a trained psychology assistant using the scale for the assessment of negative symptoms and positive symptoms (SANS-SAPS) (18, 19).

Thirty age- and gender-matched control participants, as well as 30 gender-matched elderly participants (>65 years of age) were recruited from the local community. They met the same exclusion criteria as the patients. They were also interviewed by a clinician to verify that they had no personal history of psychiatric disorders nor first-degree relatives with psychotic disorders and that they were not using any psychotropic medication.

PURSUIT TASK SET UP

Based on the classical rotary pursuit task (20), our pursuit rotor (PR) continuous sensorimotor tasks required subjects to follow the movements of a target circle (12 mm in diameter) on the computer screen with a cursor they could control by manipulating a pressure-sensitive pen on a digitizing writing tablet (WACOM1218RE), recording at 200 Hz frequency and 0.2 mm spatial accuracy.

In the circle pursuit (CPR) task, the target circle rotates along a predictable circular path with a radius of 7.5 cm (see **Figure 1**). This task consisted of two trials of 30 s duration with six rotations each. The speed of the target was gradually increased from 10 s per 360° rotation (6 RPM) to 3 s per full rotation (20 RPM).

The CPR was directly followed by the figure pursuit (FPR) task in which subjects had to follow a trajectory between and around several on-screen goals (see **Figure 2**). This task can be perceived as learning to draw a complex figure in a so-called "pursuit" condition in which a person is asked to keep the pen cursor on a target

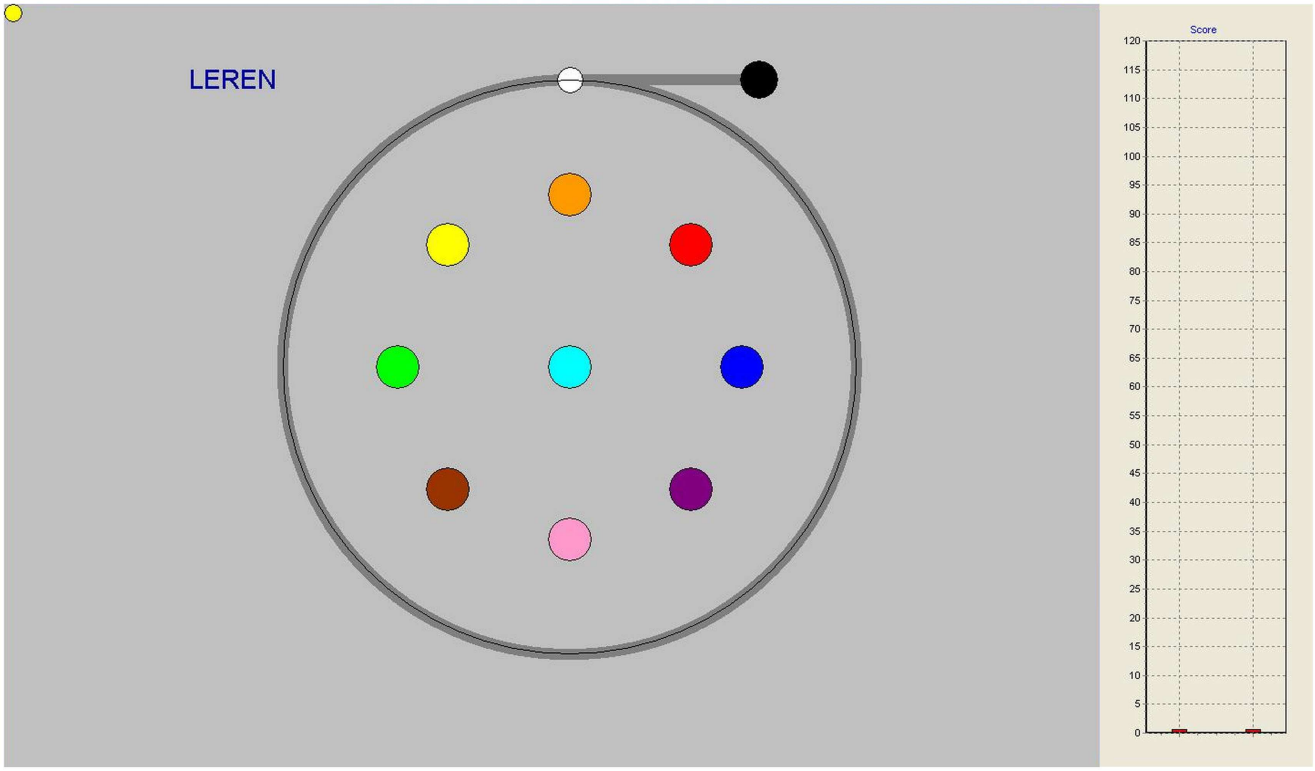


FIGURE 1 | Circle pursuit task on-screen, gray line indicating pursuit trajectory, not seen by participants. On the right-hand side, performance bars appeared as feedback after each trial.

circle that moves along the (invisible) trajectory that has to be learned. The start and end positions of the sequence are marked by white and black circles, signaling with a high and low beep, respectively, when the cursor reaches them. This task consisted of eight identical trials of 10 s duration.

Both during circle and figure pursuit, subjects were able to follow their level of performance throughout the task, with vertical score bars appearing on the right side of the screen after each trial, indicating their relative level of target contact (see **Figures 1** and **2**).

The dependent variable in both task variations was accuracy (% of time that the cursor is within the target circle, higher numbers indicating better performance). The total time of the PR tasks was approximately 3 min.

STATISTICAL ANALYSIS

We performed all statistical analyses in IBM SPSS Statistics for Windows, Version 22.0 (Armonk, NY, USA). Demographic features and baseline assessment results were analyzed using independent samples T-tests to evaluate significant group differences. There were some missing data for the Y group on the LCT ($n = 3$) and for the E group on the WCST ($n = 2$) and the LNS ($n = 1$). WCST outcome was defined as the number of categories completed. The movement time (MT) on the LCT was chosen as the relevant outcome measure for psychomotor speed.

The PR performance was quantified by the variable accuracy, and measured in three groups (schizophrenia patients = S, young controls = C, elderly participants = E). We tested each individual repeatedly in three sessions (day 1, day 2, day 7). Within each session, several identical trials were performed (two trials in CPR, eight trials in FPR). There were no missing data on the PR tasks. To provide a measure for the amount of learning over sessions, we computed two learning measures for each session: the mean and the cumulative learning gain, the latter correcting for the participant's starting level (performance on the first trial in the first session). In the figure pursuit, the cumulative learning gain was calculated as (T1 + T2 + T3 + T4 + T5 + T6 + T7 + T8)/8-S1T1. In circle pursuit, this was (T1 + T2)/2-S1T1.

We analyzed the PR data using a general linear model (GLM) with repeated measures. Because the time variable is accounted for by two separate variables in our study design, we first conducted an overall analysis with two within-subjects factors (SessionNumber, TrialNumber) and one between-subjects factor (Group, three levels). A *post hoc* analysis was used to contrast the three study groups, using Bonferroni correction to adjust for multiple comparisons (Analyses 1 and 2).

In the second step, we applied separate GLM repeated measures analyses to compare the learning over trials of groups Y–S and Y–E within the first session, which we expected to express the greatest learning effect. Subsequently, we compared the between-subjects effects of group in this analysis to the effects of group in a second analysis accounting for a covariate variable that was expected to influence the between-group differences (Analyses 3 and 4).

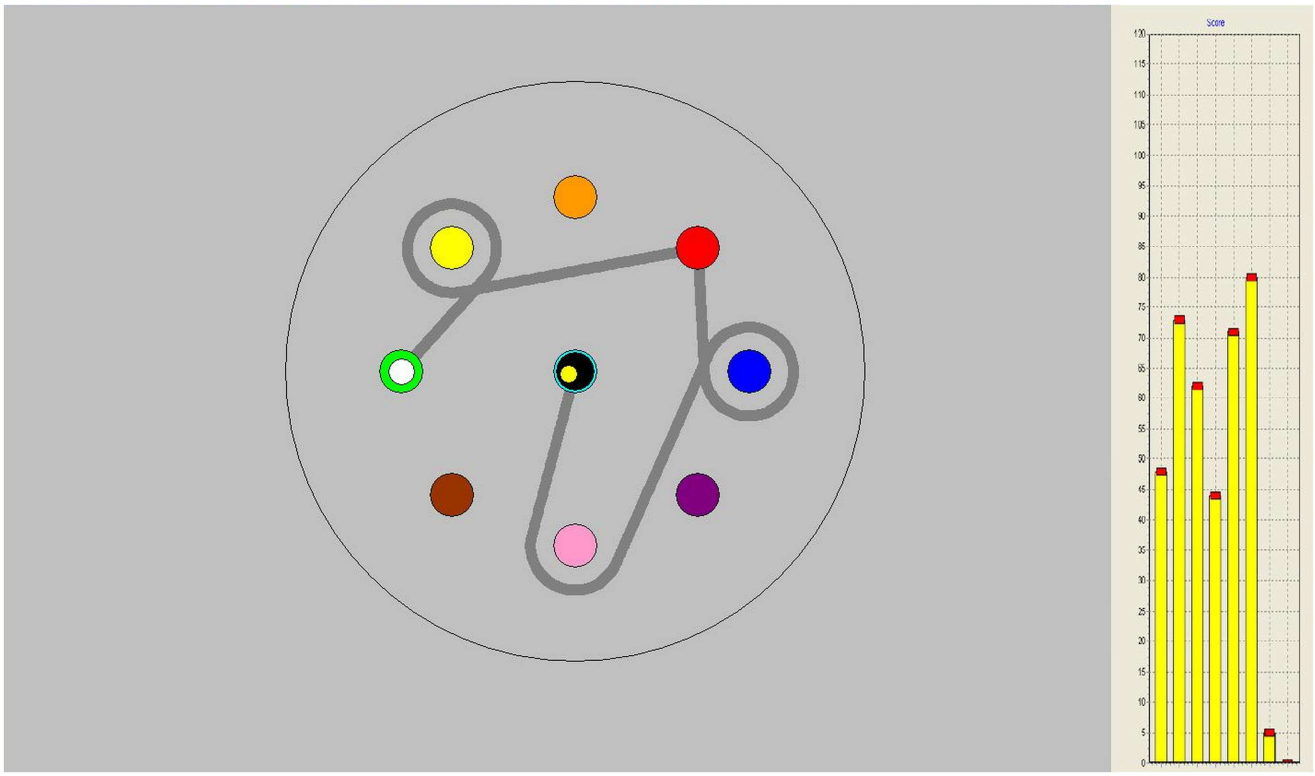


FIGURE 2 | Figure pursuit task on-screen, gray line indicating pursuit trajectory, not seen by participants. On the right-hand side, performance bars appeared as feedback after each trial.

Table 2 | Demographic and baseline assessment results.

	Schizophrenia patients (S)	Young controls (Y)	Elderly participants (E)	*T*-test S–Y	*T*-test E–Y
N	30	30	30	Matched	Matched
Age; mean (range)	36.4 (23–53)	37.3 (18–52)	69.2 (65–79)	$t(58) = 0.16$; $p = 0.875$	$t(58) = 18.99$; $p < 0.001$**
Sex M:F	20:10	20:10	20:10	Matched	Matched
Education years; mean (SD)	12.2 (±2.4)	15.1 (±2.6)	14.5 (±3.4)	$t(58) = 4.50$; $p < 0.001$**	$t(58) = 0.74$; $p = 0.465$
NLV Premorbid IQ; mean (SD)	101.30 (±10.29)	110.07 (±6.39)	111.73 (±6.43)	$t(58) = 3.96$; $p < 0.001$**	$t(58) = 1.01$; $p = 0.318$
LCT movement time; mean (SD)	0.36 (±0.15)	0.27 (±0.12)	0.40 (±0.13)	$t(55) = 2.40$; $p = 0.020$*	$t(55) = 3.65$; $p = 0.001$**
WCST categories completed; median (range)	3 (0–5)	5 (0–5)	3 (0–6)	$t(58) = 2.60$; $p = 0.012$*	$t(56) = 3.35$; $p = 0.001$**

NLV, Dutch adult reading test/Nederlandse Leestest voor Volwassenen; LCT, line-copying task); WCST, Wisconsin card sorting test.
*T-test differences are reported as t(df) and p-values (*significant at the 0.05 level; **significant at the 0.01 level).*

This procedure was repeated for three different covariates: LCT movement time (LCT_MT, an estimate of motor speed), WCST categories completed (WCST_cat, a measure of executive functioning), and education years.

In the third step, we used the computed learning measures (mean and cumulative learning gain) in separate GLM repeated measures analyses to evaluate the learning across sessions between groups Y–S and Y–E (Analyses 5 and 6).

RESULTS

DEMOGRAPHICS AND BASELINE ASSESSMENTS

Demographic features, baseline assessment results and group differences are summarized in **Table 2**. Schizophrenia patients (S) had a significantly lower level of education and premorbid IQ compared to the young controls (Y), whereas the young controls and elderly participants (E) did not differ significantly for this parameter. The Y group significantly outperformed both E and S

Table 3 | Antipsychotic drug prescriptions in schizophrenia patients.

Antipsychotic drug name	Number of prescriptions	Dose range
Clozapine	8	50–700 mg/day
Amisulpiride	7	200–800 mg/day
Haloperidol decanoate	7	75–200 mg/month
Quetiapine	6	50–600 mg/day
Olanzapine	3	5–20 mg/day
Paliperidone	3	3–6 mg/day
Paliperidone depot	3	75–200 mg/month
Aripiprazole	2	10–30 mg/day
Olanzapine depot	2	210–405 mg/month
Risperidone depot	2	50 mg/month
Clotiapine	1	40 mg/day
Flupentixol	1	1 mg/day
Bromperidol decanoate	1	125 mg/month
Zuclopentixol depot	1	200 mg/month
Risperidone	1	4 mg/day

groups on the LCT and WCST measures (see **Table 2**). Composite symptom scores for schizophrenia patients were 25.67 ± 17.39 on the SANS scale and 14.24 ± 19.68 on the SAPS scale. A summary of the use of antipsychotic drugs in schizophrenia patients included in the study is provided in **Table 3**.

ANALYSES OF CIRCLE AND FIGURE PURSUIT

Learning the PR tasks over all trials and sessions

In Analysis 1, independent of groups, learning effects were demonstrated by significant main effects of TrialNumber and SessionNumber and a significant interaction TrialNumber* SessionNumber both in the CPR task and the FPR task, indicating that the learning curves over trials for each session were different [see **Table 4A**].

Upon addition of Group as between-subjects factor in analysis 2, in both PR tasks, a significant main effect of Group was found [see **Table 4A**]. *Post hoc* analysis with Bonferroni correction demonstrated that the performance of schizophrenia patients and elderly participants was significantly poorer than the young control subjects at all stages of the task ($p < 0.001$), and that the elderly participants were the worst performing group (E-S CPR mean difference −13.62, SE 3.11, $p < 0.001$; E-S FPR mean difference −14.42, SE 2.97, $p < 0.001$).

In contrast, the interaction of TrialNumber*SessionNumber* Group was only significant in FPR, indicating that the learning curves of the groups also followed different slopes (with significant linear, quadratic, and cubic components). In CPR, the slopes were similar for the three groups [see **Table 4A**; **Figures 3** and **4**].

Learning the PR tasks over trials within session 1

In Analysis 3, comparisons of groups Y–S and Y–E on the FPR session 1 showed both a difference in performance, indicated by the significant between-subjects effect of the Group variable, as well as a different learning slope over trials, indicated by the significant TrialNumber*Group interaction. However, the significant Y–S group effect was reduced to a non-significant value when accounting for significant covariates: LCT_MT, WCST_cat, and education years in Analysis 4 [see **Table 4B**]. Combination of two individually significant covariates (LCT_MT plus WCST_cat and LCT_MT plus education years) further reduced the FPR Group effect.

In CPR session 1, again there was only a significant between-subjects effect of Group without TrialNumber*Group interaction. Furthermore, only the WCST_cat covariate reached a level of significance in the between-groups effect in this task, reducing also the Group difference between Y and S to a non-significant level [see **Table 4B**].

Interestingly, when these same covariates were added to the Y–E comparison, in both PR tasks the between-subjects Group effect remained significant [see **Table 4B**].

None of the analyses with covariates demonstrated a significant TrialNumber*Covariate or Group*Covariate interaction, suggesting the main effects of the covariates on the Accuracy variable can be interpreted independently of Group or Trialnumber.

Learning the PR tasks over sessions

The mean accuracy over trials was compared across sessions 1–3 in Analysis 5. In both PR tasks, a difference in performance between Y–S and Y–E groups was observed (i.e., significant main between-subjects effect of Group), but the SessionNumber*Group interaction was only significant for Y–E comparison, suggesting that schizophrenia patients showed a similar learning pattern across sessions as did young controls, but elderly participants did not [see **Table 4C**; **Figures 5** and **6**].

In Analysis 6, the same analyses were repeated with the learning measure cumulative learning gain, which corrects the mean for the participant's starting level performance on the first trial in session 1. Here, when Y and S groups were compared, neither the SessionNumber*Group interaction nor the between-subjects effect of Group was significant in either of the PR tasks. In the comparison of Y and E groups, a significant interaction of SessionNumber*Group was maintained for both PR tasks, but the main effect of Group was only significant for FPR [see **Table 4C**; **Figures 3** and **4**].

DISCUSSION

KEY RESULTS

General performance

Our results demonstrate poorer performance both in schizophrenia patients and in elderly participants compared to young controls, thereby matching findings of previous rotary pursuit studies (8, 11, 12, 14, 15, 17). This finding was observed in both pursuit tasks, and both on a within- and across-session level.

In FPR session 1, the poorer performance in patients was found to be attributable to differences in other functional parameters, such as psychomotor speed (LCT_MT), executive functioning (WCST categories completed), and years of education, with an additive effect. This implies that patients performing worse than healthy controls on the FPR task also perform worse on one or several of these baseline measures. One could thus hypothesize that the impaired FPR performance of patients is caused by reduced psychomotor speed and/or executive functioning or a lower level of education. Alternatively, it could also point out the existence of

Table 4 | Results of the GLM repeated measures analyses.

		Figure pursuit		Circle pursuit	
		***F* (hypothesis df, error df)[a]**	***p***	***F* (hypothesis df, error df)[a]**	***p***
(A) Y, S, AND E GROUPS					
SessionNumber[b]		285.76 (2, 88)	<0.001**	173.36 (2, 88)	<0.001**
TrialNumber[b]		179.77 (7, 83)	<0.001**	140.82 (1, 89)	<0.001**
SessionNumber*TrialNumber[b]		4.17 (14, 76)	<0.001**	13.34 (2, 88)	<0.001**
Group[c]		31.59	<0.001**	30.80	<0.001**
SessionNumber*TrialNumber*Group[c]		1.97 (28, 148)	0.005**	0.54 (4, 172)	0.710
(B) SESSION 1, Y GROUP – S GROUP					
TrialNumber*Group[d]		2.80 (7, 52)	0.015*	0.07 (1, 58)	0.799
Group[d]		7.80	0.007**	6.51	0.013*
WITH COVARIATE					
WCST_cat	Covariate[e]	19.42	<0.001**	9.35	0.003**
	Group[e]	4.57	0.114	2.54	0.117
LCT_MT	Covariate[e]	7.32	0.009**	3.15	0.082
	Group[e]	2.98	0.090	3.03	0.087
Education years	Covariate[e]	4.97	0.030*	2.18	0.146
	Group[e]	1.82	0.183	1.84	0.181
WCST(1) + LCT_MT(2)	Covariate1[e]	16.33	<0.001**		
	Covariate2[e]	5.84	0.010**		
	Group[e]	0.67	0.418		
Education years (1) + LCT_MT(2)	Covariate1[e]	5.48	0.023*		
	Covariate2[e]	8.86	0.004**		
	Group[e]	0.17	0.685		
SESSION 1, Y GROUP – E GROUP					
	TrialNumber*Group[d]	3.42 (7, 52)	0.004**	0.08 (1, 58)	0.775
	Group[d]	85.77	<0.001**	43.63	<0.001**
WITH COVARIATE					
WCST_cat	Covariate[e]	9.01	0.004**	6.84	0.011*
	Group[e]	61.35	<0.001**	27.38	<0.001**
LCT_MT	Covariate[e]	5.24	0.024*	0.61	0.439
	Group[e]	52.51	<0.001**	27.55	<0.001**
(C) LEARNING MEASURE OVER SESSIONS					
Mean	Y, S, and E groups				
	SessionNumber*Group[f]	2.51 (4, 172)	0.043*	1.59 (4, 172)	0.179
	Group[f]	31.59	<0.001**	30.80	<0.001**
	Y group – S group				
	SessionNumber*Group[f]	0.10 (2, 57)	0.905	0.87 (2, 57)	0.424
	Group[f]	9.16	0.004**	11.74	0.001**
	Y group – E group				
	SessionNumber*Group[f]	3.42 (2, 57)	0.039*	3.19 (2, 57)	0.049*
	Group[f]	83.78	<0.001**	70.26	<0.001**

(Continued)

Table 4 | Continued

		Figure pursuit		Circle pursuit	
		***F* (hypothesis df, error df)[a]**	***p***	***F* (hypothesis df, error df)[a]**	***p***
Cumulative learning gain	Y, S, and E groups				
	SessionNumber*Group[g]	2.51 (4, 172)	0.043*	1.59 (4, 172)	0.179
	Group[g]	7.81	0.001**	1.54	0.220
	Y group – S group				
	SessionNumber*Group[g]	0.10 (2, 57)	0.905	0.87 (2, 57)	0.424
	Group[g]	1.04	0.312	1.50	0.225
	Y group – E group				
	SessionNumber*Group[g]	3.42 (2, 57)	0.039*	3.19 (2, 57)	0.049*
	Group[g]	16.23	<0.001**	0.269	0.107

[a]*Wilk's Lambda F for multivariate analysis results.*

[b]*Analysis 1: within-subjects factors SessionNumber(3) and TrialNumber (8 FPR; 2 CPR).*

[c]*Analysis 2: within-subjects factors SessionNumber(3) and TrialNumber (8 FPR; 2 CPR) and between-subjects factor Group (3).*

[d]*Analysis 3: within-subjects factor TrialNumber (8 FPR; 2 CPR) and between-subjects factor Group (2).*

[e]*Analysis 4: within-subjects factor TrialNumber (8 FPR; 2 CPR), between-subjects factor Group (2) and covariate.*

[f]*Analysis 5: within-subjects factor SessionNumber(3), between-subjects factor Group (3 or 2), variable mean.*

[g]*Analysis 6: within-subjects factor SessionNumber(3), between-subjects factor Group (3 or 2), variable cumulative learning gain.*

**Significant at the 0.05 level; **significant at the 0.01 level.*

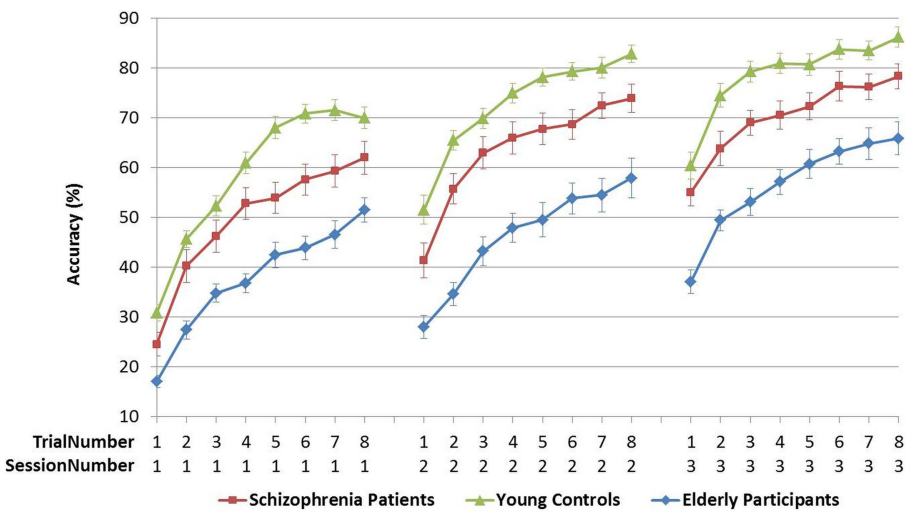


FIGURE 3 | Figure pursuit accuracy over three sessions and eight trials.

a separate subgroup of schizophrenia patients exhibiting impairments on all of these domains. In contrast, the difference in FPR performance between elderly participants and young controls could not be accounted for by differences in psychomotor speed nor executive functioning, indicating a performance gap between these groups that is independent of other functional parameters.

In CPR, contrasting to what was expected, psychomotor speed did not have a significant effect on the performance in session 1. Only executive functioning level appeared to account significantly for the difference between schizophrenia patients and controls in this task.

After the mean performance per session was corrected for the initial starting level, there was no longer a significant difference in performance across sessions between patients and controls. This finding suggests that the lower mean performance of patients is caused by a significantly lower starting level, which is not recovered by additional practice. However, in two other recent PR studies,

an individual equation of the target speed was applied to account for participants' starting level performance; yet, the general performance in schizophrenia patients was found to be impaired nonetheless (12, 15). Thus, adjusting the difficulty of the task does not seem to solve the performance gap. Further study is needed to understand these seemingly contradictory findings. Regarding the elderly participants, their poorer mean level of performance was amended in the CPR, but remained in the FPR after correction for their significantly lower starting level by the cumulative learning gain measure.

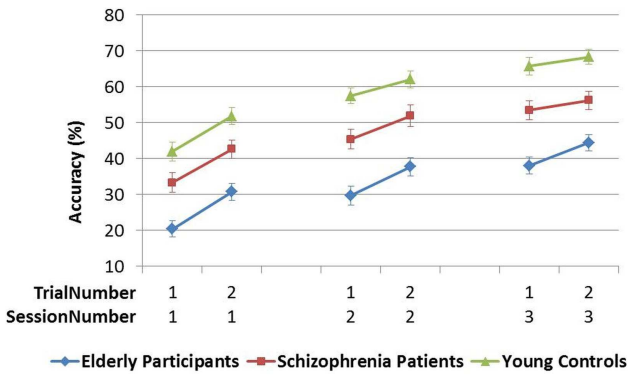


FIGURE 4 | Circle pursuit accuracy over three sessions and two trials.

Skill learning rate

We have established that all groups learned the new FPR and CPR sensorimotor skills over trials and sessions, but whereas the overall learning rate of schizophrenia patients and elderly participants was preserved in CPR, it differed between the three groups in FPR.

The early phase of learning the FPR skill was characterized by a significantly different learning curve of the schizophrenia patients and the elderly participants compared to young controls, who reached their peak performance earlier, as illustrated in **Figure 3**. The CPR consisted of only two trials in the first session, and therefore by definition the learning rate was marked by a linear increase, of which the slopes did not differ between the three groups (see **Figure 4**). In the later phase of learning of both PR tasks, schizophrenia patients and control subjects showed comparable learning gains over sessions, but elderly participants learned significantly less.

STUDY LIMITATIONS

By using two variations of the PR task, we have attempted to distinguish motor and sequence learning components, yet it remains difficult to single out and evaluate separately the processes involved in sensorimotor learning and performance. We cannot rule out the impact of declarative and spatial memory, attention capacity, and motor coordination on our PR skill performance and learning results. Also, while our CPR task was similar to the classical rotary pursuit task, we used a different methodology regarding the number of trials and rotation speed (see **Table 1**), which complicates the comparison of our results in the CPR to

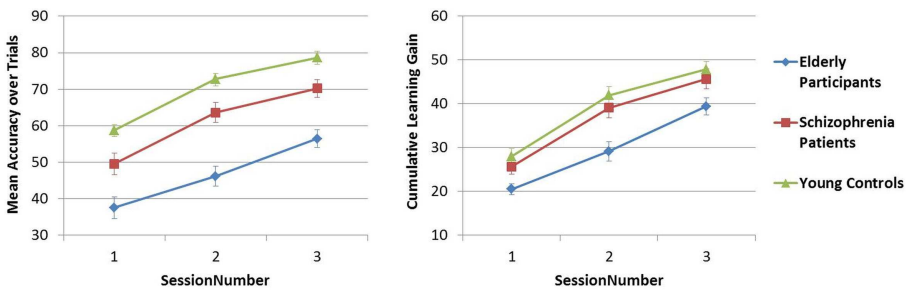


FIGURE 5 | Figure pursuit mean accuracy and cumulative learning gain over three sessions.

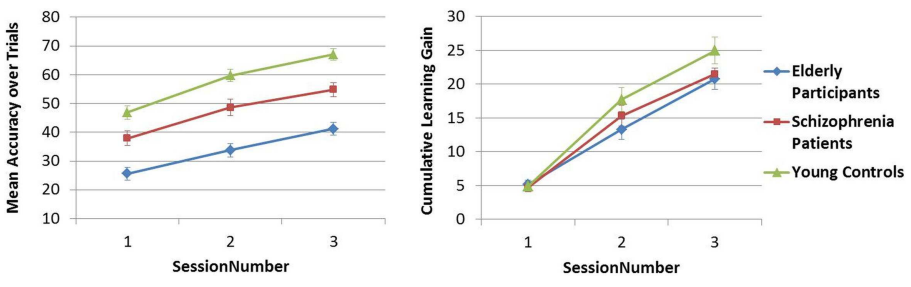


FIGURE 6 | Circle pursuit mean accuracy and cumulative learning gain over three sessions.

those of previous PR studies. It is possible that the number of trials per session in our CPR was too limited to establish within-session learning differences, which were found in FPR but not in CPR.

This study included only schizophrenia outpatients who were able to complete the test batteries and results can, therefore, not necessarily be generalized to the whole population of patients with schizophrenia. However, the mean SAPS and SANS composite scores in our sample concurred with scores found by van Erp et al. in a sample of 205 schizophrenia patients: mean composite SAPS 16.8 ± 14.2 compared to 14.2 ± 19.7 in our sample, and mean composite SANS 23.0 ± 14.6 compared to 25.7 ± 17.4 in our sample (21). Our patient population can, therefore, not be presumed to differ significantly in terms of symptom severity from other schizophrenia patient samples.

A large within-group heterogeneity in performance existed, particularly in the starting performance level of schizophrenia patients and the final performance level of elderly subjects. The relatively higher performance heterogeneity of the patients and elderly participants compared to the young controls may imply performance on the PR tasks in these groups was influenced by other variables than those accounted for in our study design. Problems with the evaluation of cognition of schizophrenia patients include lack of motivation and attention problems caused by negative symptomatology. Patients were instructed to complete the tasks to the best of their ability and our experience during test procedures was that being able to follow the feedback of their performance live on-screen provided an additional stimulus for performance optimization to subjects in all groups.

Other variables that may affect task performance include general cognitive functioning and medication use. We did not evaluate the study groups for their current IQ scores, and the schizophrenia patients had a significantly lower premorbid IQ score compared to young and elderly controls. In previous studies, comparing IQ-matched subgroups reduced or abolished differences in the overall level of performance between schizophrenic patients and control subjects on the rotor pursuit and other tasks of procedural learning (14, 15). However, IQ matching may also introduce a bias, considering research of general intelligence in schizophrenia has shown that only about a quarter of schizophrenia patients have a preserved IQ compared to the general population (22). Moreover, correlations between motor and cognitive functioning in schizophrenia patients have been repeatedly demonstrated (23, 24), and matching for cognitive parameters in studies of motor learning may, therefore, greatly influence the primary outcome measure. It is often argued that cognitive impairments in schizophrenia, and specifically psychomotor ones, are caused by psychotropic substances in general and antipsychotic medication in particular. All patients in our study had been stably treated with antipsychotic medication at the time of testing, and 16 patients were using more than one antipsychotic drug concomitantly (see **Table 3**). The reduced performance on PR tasks combined with a normal learning rate in patients may be hypothesized to be due to the use of antipsychotic drugs, known to affect psychomotor functioning (25).

IMPLICATIONS FOR FUTURE RESEARCH AND CLINICAL PERSPECTIVES

Our study provides important caveats toward future research on procedural learning in schizophrenia. Researchers should be aware that motor tasks including a sequence component should be distinguished from true motor learning tasks. As shown in this study, small variations applied to commonly used procedural tasks may allow to distinguish between operationally different components that may be important to further elucidate the nature of the deficits in schizophrenia. Particularly, the combination of different sensorimotor learning tasks with imaging techniques can be valuable to evaluate structural and functional brain alterations in the motor system. Furthermore, a longitudinal design should be a key feature of any study design interested in aspects of learning and memory, with differentiation of early and late learning phases.

Cognitive functioning, and specifically also executive functioning as measured with the Wisconsin card sorting test, has been shown to be a major predictor of functional outcome in schizophrenia (1). Motor learning in schizophrenia has been less studied, and its relation to functional outcome is currently unknown. However, evidence that motor performance is not only related to cognitive and executive functioning but also a predictor of cognitive deficits in schizophrenia patients at 1-year follow-up (23) suggests an association between motor performance or learning capacity, and functional outcome may exist that merits further investigation.

An age-related decline in sensorimotor learning has been previously recognized (17, 26), and in our study indeed the elderly participants demonstrated both poorer performance and lower learning gains in both PR tasks. Unexpectedly, the schizophrenia patients even outperformed the elderly healthy participants. Although this finding needs to be confirmed, it governs a more optimistic message about the functioning of patients than has hitherto been assumed. However, it is uncertain whether this pattern is maintained throughout different cognitive domains. Findings of our research group, as reported elsewhere in this journal (Cornelis et al., in press), suggest that in other cognitive domains, elderly participants may outperform schizophrenia patients. It might be interesting for future studies to include both elderly and non-elderly schizophrenia and control participants to differentiate between the mechanisms of cognitive impairment related to aging and schizophrenia.

A generally lower level of performance in schizophrenia (starting and ending the learning phase at a lower level than control subjects) has been a frequent finding in PR studies (11, 12, 14). Some authors have interpreted this phenomenon as reflecting impaired procedural learning in schizophrenia patients. However, since this reduced overall level of performance is usually accompanied with a normal learning rate, the mechanisms that underlie these two aspects of task performance are likely to differ to some extent. Because of this difficulty to differentiate between y-intercept (absolute performance) and slope (learning rate), and because of the high degree of within-group heterogeneity on performance level, many studies have not been able to conclude as to the actual capacity for sensorimotor skill learning of schizophrenia patients. Based on our results, it seems that schizophrenia patients have a mostly preserved capacity to learn sensorimotor

skills, with any deficit related more to the early learning phase of sequence-holding skills and depending largely on the starting level performance of patients. This knowledge may prove important to the development and evaluation of therapies to improve such deficits in schizophrenia, in which the rotary pursuit, a well-established, easy and quick to administer task, may be used for the initial and follow-up evaluation of motor learning capacity and performance in patients. Because the late-phase learning of patients was preserved, it can be suspected that with an extended number of trials, the patients could eventually reach the same performance level as the final level in young controls. Thus, schizophrenia patients maintain the ability to acquire new skills, of vital importance to everyday functioning, given extra room for rehearsal. On the other hand, since more complex skills often also require additional cognitive components related to planning and organization, it is unclear whether this finding may be translated to all real-life skills.

CONCLUSION

Both in circle pursuit (motor task) and figure pursuit (motor plus sequence task), learning was evident in all groups, with equal learning gains of schizophrenia patients compared to age-matched controls, but reduced learning in elderly participants. In terms of general performance, the schizophrenia patients fell between the young controls and the elderly participants, differing significantly from both. Our results suggest that the lower performance of schizophrenia patients compared to age-matched controls can be accounted for by impaired speed of movement and executive functioning.

AUTHOR CONTRIBUTIONS

All the authors met ICMJE criteria and all those who fulfilled those criteria were listed as authors. All the authors had access to the study data and made the final decision about where to present these data.

ACKNOWLEDGMENTS

This clinical trial was sponsored by Janssen Research and Development, Janssen Pharmaceutica N.V. (Beerse, Belgium). The authors would like to thank Ms. Apers, Ms. Laureys, and Ms. Vermeylen for their support in the testing of the study participants. The authors also thank the study participants, without whom the studies would never have been accomplished. The study is registered at ClinicalTrials.gov: NCT01788436.

REFERENCES

1. Green MF, Kern RS, Heaton RK. Longitudinal studies of cognition and functional outcome in schizophrenia: implications for MATRICS. *Schizophr Res* (2004) **72**:41–51. doi:10.1016/j.schres.2004.09.009
2. Squire LR. Declarative and nondeclarative memory: multiple brain systems supporting learning and memory. *J Cogn Neurosci* (1992) **4**:232–43. doi:10.1162/jocn.1992.4.3.232
3. Marsh R, Alexander GM, Packard MG, Zhu H, Peterson BS. Perceptual-motor skill learning in Gilles de la Tourette syndrome. Evidence for multiple procedural learning and memory systems. *Neuropsychologia* (2005) **43**:1456–65. doi:10.1016/j.neuropsychologia.2004.12.012
4. Ammons RB. Acquisition of motor skill; rotary pursuit performance with continuous practice before and after a single rest. *J Exp Psychol* (1947) **37**:393–411. doi:10.1037/h0054334
5. Roth RM, Baribeau J, Milovan D, O'Connor K, Todorov C. Procedural and declarative memory in obsessive-compulsive disorder. *J Int Neuropsychol Soc* (2004) **10**:647–54. doi:10.1017/S1355617704105018
6. Graybiel AM, Aosaki T, Flaherty AW, Kimura M. The basal ganglia and adaptive motor control. *Science* (1994) **265**:1826–31. doi:10.1126/science.8091209
7. Doyon J, Bellec P, Amsel R, Penhune V, Monchi O, Carrier J, et al. Contributions of the basal ganglia and functionally related brain structures to motor learning. *Behav Brain Res* (2009) **199**:61–75. doi:10.1016/j.bbr.2008.11.012
8. Huston P, Shakow D. Learning capacity in schizophrenia. *Am J Psychiatry* (1949) **105**:881–8.
9. Goldberg TE, Torrey EF, Gold JM, Ragland JD, Bigelow LB, Weinberger DR. Learning and memory in monozygotic twins discordant for schizophrenia. *Psychol Med* (1993) **23**:71–85. doi:10.1017/S0033291700038861
10. Granholm E, Bartzokis G, Asarnow RF, Marder SR. Preliminary associations between motor procedural learning, basal ganglia T2 relaxation times, and tardive dyskinesia in schizophrenia. *Psychiatry Res* (1993) **50**:33–44. doi:10.1016/0925-4927(93)90022-A
11. Clare L, McKenna PJ, Mortimer AM, Baddeley AD. Memory in schizophrenia: what is impaired and what is preserved? *Neuropsychologia* (1993) **31**:1225–41. doi:10.1016/0028-3932(93)90070-G
12. Schwartz BL, Rosse RB, Veazey C, Deutsch SI. Impaired motor skill learning in schizophrenia: implications for corticostriatal dysfunction. *Biol Psychiatry* (1996) **39**:241–8. doi:10.1016/0006-3223(95)00130-1
13. Kern R, Green M, Wallace C. Declarative and procedural learning in schizophrenia: a test of the integrity of divergent memory systems. *Cogn Neuropsychol* (1997) **2**:39–50. doi:10.1080/135468097396405
14. Weickert TW, Terrazas A, Bigelow LB, Malley JD, Hyde T, Egan MF, et al. Habit and skill learning in schizophrenia: evidence of normal striatal processing with abnormal cortical input. *Learn Mem* (2002) **9**:430–42. doi:10.1101/lm.49102
15. Gomar JJ, Pomarol-Clotet E, Sarro S, Salvador R, Myers CE, McKenna PJ. Procedural learning in schizophrenia: reconciling the discrepant findings. *Biol Psychiatry* (2011) **69**:49–54. doi:10.1016/j.biopsych.2010.07.013
16. Gold JM, Hahn B, Strauss GP, Waltz JA. Turning it upside down: areas of preserved cognitive function in schizophrenia. *Neuropsychol Rev* (2009) **19**:294–311. doi:10.1007/s11065-009-9098-x
17. Kennedy KM, Partridge T, Raz N. Age-related differences in acquisition of perceptual-motor skills: working memory as a mediator. *Neuropsychol Dev Cogn B Aging Neuropsychol Cogn* (2008) **15**:165–83. doi:10.1080/13825580601186650
18. Andreasen N. *The Scale for the Assessment of Negative Symptoms (SANS)*. Iowa City, Iowa: University of Iowa (1983).
19. Andreasen N. *The Scale for the Assessment of Positive Symptoms (SAPS)*. Iowa City, Iowa: University of Iowa (1984).
20. Siegel D. A multivariate study of pursuit rotor skill development. *Res Q Exerc Sport* (1990) **61**:201–5. doi:10.1080/02701367.1990.10608676
21. van Erp TG, Preda A, Nguyen D, Faziola L, Turner J, Bustillo J, et al. Converting positive and negative symptom scores between PANSS and SAPS/SANS. *Schizophr Res* (2014) **152**:289–94. doi:10.1016/j.schres.2013.11.013
22. Weickert TW, Goldberg TE, Gold JM, Bigelow LB, Egan MF, Weinberger DR. Cognitive impairments in patients with schizophrenia displaying preserved and compromised intellect. *Arch Gen Psychiatry* (2000) **57**:907–13. doi:10.1001/archpsyc.57.9.907
23. Salazar-Fraile J, Balanza-Martinez V, Selva-Vera G, Martinez-Aran A, Sanchez-Moreno J, Rubio C, et al. Motor speed predicts stability of cognitive deficits in both schizophrenic and bipolar I patients at one-year follow-up. *Eur J Psychiatry* (2009) **23**:184–97. doi:10.4321/S0213-61632009000300007
24. Cuesta MJ, Sanchez-Torres AM, de Jalon EG, Campos MS, Ibanez B, Moreno-Izco L, et al. Spontaneous parkinsonism is associated with cognitive impairment in antipsychotic-naive patients with first-episode psychosis: a 6-month follow-up study. *Schizophr Bull* (2014) **40**:1164–73. doi:10.1093/schbul/sbt125
25. Morrens M, Hulstijn W, Sabbe B. The effects of atypical and conventional antipsychotics on reduced processing speed and psychomotor slowing in schizophrenia: a cross-sectional exploratory study. *Clin Ther* (2008) **30**:684–92. doi:10.1016/j.clinthera.2008.04.012
26. Ghisletta P, Kennedy KM, Rodrigue KM, Lindenberger U, Raz N. Adult age differences and the role of cognitive resources in perceptual-motor skill acquisition: application of a multilevel negative exponential model. *J Gerontol B Psychol Sci Soc Sci* (2010) **65B**:163–73. doi:10.1093/geronb/gbp126

Conflict of Interest Statement: This clinical trial received funding support by Janssen Research & Development, a division of Janssen Pharmaceutica N.V., Beerse, Belgium. The co-authors Luc Janssens and Maarten Timmers are employees of Janssen Research & Development, a division of Janssen Pharmaceutica N.V., Beerse, Belgium, and own stock/stock options in the company.

Received: 01 October 2014; accepted: 06 November 2014; published online: 24 November 2014.

*Citation: De Picker LJ, Cornelis C, Hulstijn W, Dumont G, Fransen E, Timmers M, Janssens L, Morrens M and Sabbe BGC (2014) Stable schizophrenia patients learn equally well as age-matched controls and better than elderly controls in two sensorimotor rotary pursuit tasks. Front. Psychiatry **5**:165. doi: 10.3389/fpsyt.2014.00165*

This article was submitted to Schizophrenia, a section of the journal Frontiers in Psychiatry.

frontiers in
PSYCHIATRY

REVIEW ARTICLE
published: 25 November 2014
doi: 10.3389/fpsyt.2014.00160

Cerebellar-motor dysfunction in schizophrenia and psychosis-risk: the importance of regional cerebellar analysis approaches

Jessica A. Bernard*[1] *and Vijay A. Mittal*[1,2]

[1] *Department of Psychology and Neuroscience, University of Colorado Boulder, Boulder, CO, USA*
[2] *Center for Neuroscience, University of Colorado Boulder, Boulder, CO, USA*

Edited by:
Manuel Morrens, University of Antwerp, Belgium

Reviewed by:
Bernhard J. Mitterauer, University of Salzburg, Austria
Sebastian Walther, University Hospital of Psychiatry, Switzerland
Manuel Morrens, University of Antwerp, Belgium

****Correspondence:***
Jessica A. Bernard, Department of Psychology and Neuroscience, University of Colorado Boulder, 345 UCB, Boulder, CO 80309-0345, USA
e-mail: jessica.bernard@colorado.edu

Motor abnormalities in individuals with schizophrenia and those at-risk for psychosis are well documented. An accumulating body of work has also highlighted motor abnormalities related to cerebellar dysfunction in schizophrenia including eye-blink conditioning, timing, postural control, and motor learning. We have also recently found evidence for motor dysfunction in individuals at ultra high-risk for psychosis (1–3). This is particularly relevant as the cerebellum is thought to be central to the cognitive dysmetria model of schizophrenia, and these overt motor signs may point to more general cerebellar dysfunction in the etiology of psychotic disorders. While studies have provided evidence indicative of motor cerebellar dysfunction in at-risk populations and in schizophrenia, findings with respect to the cerebellum have been mixed. One factor potentially contributing to these mixed results is the whole-structure approach taken when investigating the cerebellum. In non-human primates, there are distinct closed-loop circuits between the cerebellum, thalamus, and brain with motor and non-motor cortical regions. Recent human neuroimaging has supported this finding and indicates that there is a cerebellar functional topography (4), and this information is being missed with whole-structure approaches. Here, we review cerebellar-motor dysfunction in individuals with schizophrenia and those at-risk for psychosis. We also discuss cerebellar abnormalities in psychosis, and the cerebellar functional topography. Because of the segregated functional regions of the cerebellum, we propose that it is important to look at the structure regionally in order to better understand its role in motor dysfunction in these populations. This is analogous to approaches taken with the basal ganglia, where each region is considered separately. Such an approach is necessary to better understand cerebellar pathophysiology on a macro-structural level with respect to the pathogenesis of psychosis.

Keywords: cerebellum, schizophrenia, psychosis-risk, motor abnormalities, balance, timing, morphology, motor learning

INTRODUCTION

Schizophrenia is a devastating mental illness marked by a variety of symptoms, including positive symptoms (hallucinations and delusions) and negative symptoms (anhedonia and social withdrawal) (5). In addition to the classic symptoms, these patients also exhibit movement abnormalities as well as cognitive and affective dysfunction. These movement abnormalities are in a variety of domains and include dyskinesias (6), as well as psychomotor slowing, catatonia, neurological soft signs, extrapyramidal signs, and motor learning deficits (7–10). Psychosis has been studied as a spectrum disorder, with investigations of different patient groups that show some symptoms that are associated with risk. In this review, we focus on several specific groups in addition to schizophrenia, including those at psychosis-risk, a category that can refer to genetic risk, as those with a first-degree relative with the disease are at greater risk for development of schizophrenia. In this category, there are also individuals referred to as ultra high-risk (UHR), where there are recent onset or escalating range of moderate (i.e., partially formed/occurring occasionally without full conviction or related functional impairment) positive attenuated symptoms (e.g., unusual thoughts, suspiciousness, grandiosity, perceptual anomalies, and disorganized communication) associated with decreased functionality in social relationships or day-to-day life. After a diagnosis of schizophrenia, this period of attenuated symptoms is referred to as the prodromal period. However, not all those that experience these symptoms will go on to develop schizophrenia or another psychotic disorder. Finally, there are individuals diagnosed with schizotypal personality disorder, who show trait level unusual behaviors, suspiciousness, and ideas of reference. This group is also at greater than average risk for schizophrenia. Interestingly, movement abnormalities are present in these at-risk populations as well [e.g., (1, 2, 6)].

Movement abnormalities are present as early as infancy in individuals that go on to develop schizophrenia later in life [e.g., (5)], indicating that such movement abnormalities maybe associated with the disease or disease process, as opposed to being a side-effect

of medication (11). Indeed, prior to the onset of schizophrenia, and certainly during infancy, individuals are less likely to be impacted by many of the confounding factors that could also further impact movement abnormalities associated with schizophrenia (e.g., anti-psychotic medications, drug, and alcohol use/abuse). These movement abnormalities are typically dyskinetic movements, and are thought to be related to the dopaminergic dysfunction in the basal ganglia (12), and have been previously reviewed elsewhere (6). Importantly, these motor abnormalities are present prior to disease onset, and continue across the disease course. Further supporting this, many movement abnormalities are seen in drug-naïve adults with schizophrenia as well (10).

In addition to the striatally mediated dyskinesias seen in schizophrenia and psychosis-risk groups (3, 6, 13–22) and the psychomotor slowing, catatonia, and parkinsonism (7–10), there is also evidence of cerebellar dysfunction in both schizophrenia, and psychosis-risk populations [e.g., Ref. (1–3, 17–21)]. The most prominent evidence of cerebellar dysfunction is with respect to its role in cognitive dysmetria (23–25). Andreasen and colleagues have demonstrated that there is abnormal functional activation in the cerebellum, thalamus, and cortex in patients with schizophrenia (23, 24), and more recently, there has been increased interest in the study of the cerebellum in these patients, particularly with respect to cerebello-thalamic connections (26). Cerebellar activation deficits exists across functional domains (27), and we refer readers to the review by Picard and colleagues for a detailed discussion of the cerebellum in schizophrenia, as it is beyond the scope of our review here (25).

The cerebellum is classically thought of as a brain structure that is important for motor control; however, there is a robust literature to indicate that the structure is also heavily involved in cognitive and affective processing (4, 28–33). As such, though the cerebellum and cerebello-thalamo-cortical circuit were first discussed in schizophrenia with respect to cognitive dysmetria, there is also a great deal of evidence to indicate that there are motor cerebellar deficits in schizophrenia in addition to the aforementioned dyskinesias, psychomotor slowing, catatonia, and parkinsonism. Indeed, there is also an emerging literature indicating that as with dyskinesias, cerebellar-motor abnormalities are also present in psychosis-risk populations [e.g., (1, 2)]. Thus, it may be that more overt cerebellar-motor dysfunction may also serve as a marker of disease and disease progression, such as has been proposed for striatal-mediated dyskinesias (6). This is particularly exciting, as the cerebellar–thalamic network represents a distinct mechanism, and may hold the potential to explain/predict heretofore poorly understood processes across the psychosis spectrum. Here, our goal is twofold. First, we provide a review of cerebellar–motor dysfunction in patients with schizophrenia as well as in psychosis-risk groups including genetic risk, UHR populations, and schizotypal individuals. Second, we provide a detailed overview of the cerebellar functional topography and weigh evidence in support of a targeted regional approach for cerebellar investigations. We suggest that more specific topographically informed approaches to investigating the cerebellum (particularly with respect to cerebellar morphology and cerebello-cortical networks) across the psychosis spectrum will yield informative results with respect to the involvement of the cerebellum in psychosis.

MOTOR CEREBELLAR DYSFUNCTION IN SCHIZOPHRENIA AND PSYCHOSIS-RISK

The cerebellum is important for motor function generally in that it is important for online monitoring of movements (34, 35). Eye-blink conditioning and postural control are both especially reliant upon the cerebellum, but it is also strongly engaged during motor learning, and it has been suggested that one of the primary functions of the cerebellum is in the precise timing of movements (36, 37). While the cerebellum is likely to be involved in many motor behaviors, several domains have been studied in greater depth in patients across the psychosis spectrum. We will discuss in turn eye-blink conditioning, postural control, timing, and motor learning. For each motor task paradigm, we will review the existing evidence indicating impairments across the psychosis spectrum, as well as any evidence that directly links these behaviors to the cerebellum [either structure or function as measured using functional magnetic resonance imaging (fMRI)] in these populations. A summary of performance for each task domain for both patients with schizophrenia and at-risk/psychosis spectrum populations is provided in **Table 1**. Finally, future directions for research in each domain will be discussed, particularly with respect to the study of psychosis.

EYE-BLINK CONDITIONING

Eye-blink conditioning is one of the simplest learning paradigms, and performance of this task is dependent upon the cerebellum (38–40). The circuits involved in eye-blink conditioning have been carefully mapped using animal models, but have also been extensively investigated in humans primarily in lesion studies, and both the deep cerebellar nuclei (particularly the interposed nuclei) and cerebellar cortex seemed to be important for task performance (38–40). In these paradigms, a puff of air is delivered to the eye, resulting in a blink response. During the conditioning phases, a tone precedes and typically co-terminates with the air-puff, resulting in conditioned responses (CRs). That is, individuals that learn the association between the tone and the air-puff that follows it blink their eyes at the sound of the tone. Because this is so heavily dependent upon the cerebellum, it is often used as an indicator of cerebellar function. In schizophrenia, there is a growing literature investigating performance on this task in patients.

Across the literature investigating patients with schizophrenia, the general finding is that patients are impaired in eye-blink conditioning, and show fewer CRs to the tone alone when compared with controls (40–47). During the paradigm, the percentage of CRs is significantly lower than that in controls. However, though this seems to be a relatively robust finding, there have been several studies that provide evidence to the contrary (48–51). Reasons for the mixed findings are unclear, but may be due to the heterogeneity of the patients included in these samples particularly with respect to medication, as well as differences in task design. Importantly, a recent investigation of neuroleptic naïve patients or patients that have been off medication for 3 weeks demonstrated eye-blink conditioning deficits suggesting that this impairment is not solely a function of medication status (46).

In addition to the lower percentage of CRs, there is also evidence in patients with schizophrenia to indicate that the timing of these responses is negatively impacted (41, 42, 45) (timing will also be discussed in further detail below). During the conditioning

Table 1 | Summary of findings across the reviewed motor domains for both patients with schizophrenia and high-risk groups.

Task domain	Schizophrenia deficits	High-risk deficits
Eye-blink conditioning	Poor conditioning: fewer conditioned responses to the presentation of a tone, which is followed by an aversive puff of air to the eye	Fewer and earlier conditioned responses in SPD
	Altered timing of responses so that eye does not close in time with the air-puff	Genetic risk populations also show fewer conditioned responses
Postural control	Greater postural sway indicative of poor postural control, associated with symptom severity	Increased postural sway in UHR individuals that is specifically associated with negative symptom severity
	Presence of the Romberg sign more common in patients	
Timing	Impairments in temporal bisection (time perception)	No evidence indicating sub-second cerebellar timing deficits
	Increased variability during temporal production (synchronization–continuation tasks)	Sub-second timing correlated with dimensions of schizotypy
Motor learning	Implicit and explicit sequence learning deficits such that patients learn, but to a lesser degree than controls	Deficits in pursuit rotor performance in UHR
	Relationships also seen with the cerebellum	No deficits on sequence learning in SPD

SPD, schizotypal personality disorder; UHR, ultra high-risk.

paradigms, the tone typically co-terminates with the onset of the air-puff to the eye. The optimal response is such that the anticipatory eye-blink that occurs as a result of the tone (CR) is timed so that the eye is closed upon the delivery of the air-puff. Brown and colleagues found that the timing of the CRs was more variable in patients with schizophrenia (42) while Bolbecker and colleagues reported less adaptive CRs as they occurred significantly earlier in patients when compared to controls (41). A similar trend level finding of earlier CRs in patients was found by Forsyth and colleagues (45).

Across the psychosis spectrum, there is also evidence to indicate impairments in eye-blink conditioning. Individuals with schizotypal personality disorder have deficits similar to patients with schizophrenia in that they show fewer CRs, and there is also a trend indicating altered (earlier) CR timing in this population (45). Most recently, Bolbecker and colleagues investigated eye-blink conditioning in a group of patients with schizophrenia, those at genetic risk, and healthy controls (52). Both the patient and genetic risk groups showed impaired associative learning as measured with CRs. The authors suggest that cerebellar abnormalities may be a marker of risk for schizophrenia (52). Furthermore, this provides additional support to indicate that these deficits are not an artifact of medication, as they are present in genetic risk groups.

Finally, it is of note that there have been several investigations of the cerebellum more directly with respect to eye-blink conditioning. First, Edwards and colleagues measured the volume of the anterior and posterior aspects of the cerebellum and investigated these volumes with respect to conditioning (43) in patients with schizophrenia and controls. Volume of the anterior cerebellum in patients was smaller than that of controls and the patients also showed impaired conditioning. However, there were no significant correlations between cerebellar volume and conditioning performance in patients with schizophrenia. In fact, the non-significant relationship in the patient group was in the opposite direction as that seen in the controls (43). The authors suggest that there are perhaps altered structure–function relationships in the cerebellum in patients with schizophrenia (43). However, further confirmation of these findings is necessary, particularly as only very large regions of the cerebellum were investigated.

Using positron emission tomography (PET), medication free patients with schizophrenia and controls were scanned during the eye-blink conditioning paradigm (46). Not only did the patient group show impaired associative learning, but they also showed decreased blood flow in the cerebellum and the thalamus. This indicates cerebellar dysfunction in the patient group along with the behavioral impairments (46). While this investigation and that of Edwards and colleagues are important first steps in linking cerebellar morphology and function to this overt motor impairment, it is also clear that more work is needed.

There are several key future directions for eye-blink-conditioning research. Most interestingly is the use of functional neuroimaging. While Parker and colleagues took advantage of PET imaging (46), recent advances in the technology used to deliver the air-puff and monitor the eye-blinks have allowed for investigations of this task using fMRI (53, 54). This approach has provided important insights into the cerebellum and eye-blink conditioning in normative development (54). Linking eye-blink conditioning to additional cognitive measures as well as symptomatology in disease populations is important. Several groups have started to investigate eye-blink conditioning with respect to cognition with mixed results (41, 45), and to our knowledge there have not yet been any investigations linking CRs with symptom severity. Such future work is important for our understanding of cerebellar contributions to disease and cognition, and will help us to better understand whether or not this motor measure is a reasonable marker of disease state. Lastly, investigations in UHR populations would also be especially informative. The work by Bolbecker and colleagues in genetic risk is an important first step (52), and the field would benefit from a replication and extension of this work in UHR individuals.

POSTURAL CONTROL

Postural control relies upon sensorimotor integration and vestibular function. The cerebellum has long been implicated in postural control (55). Patient studies in those with ataxia or cerebellar lesions show increased postural sway (poor postural control) (56), and the measurement of regional cerebral blood flow using PET imaging has also shown increases in blood flow in the cerebellum (57). Much like eye-blink conditioning, postural control can also be used as a potential indicator of cerebellar function. Indeed in healthy adults, balance has been linked to regional cerebellar volume (58), and similar associations between cerebellar volume and balance have been seen in alcoholism where cerebellar volume is negatively effected by the disease (59, 60).

Investigations of postural control in schizophrenia were initiated as far back as the 1940s. Using vestibular stimulation Angyl and Sherman (61) found deficits related to postural control in patients with schizophrenia. Though the methods to investigate postural control vary greatly in their sensitivity, the general finding is that patients with schizophrenia have impaired postural control. Earlier work in this domain relied primarily upon behavioral measures and assessments of balance such as judgment of the presence of the Romberg sign (loss of balance when the eyes are closed, arms are outstretched, and feet are in a heel-to-toe tandem position), or assessing the ability to stand heel-to-toe, or on one foot (62, 63). Presence of the Romberg sign is significantly more common in patients with schizophrenia as compared to healthy controls (62) and patients are also impaired at standing on one foot, and heel-to-toe standing, though this is further compounded in patients with schizophrenia that also have a history of alcoholism (63). Thus, in schizophrenia, these postural control deficits are present, and can increase in severity in cases of alcohol abuse.

More recent investigations have used instrumental measures of balance and quantify body sway. Such measures have a much higher degree of sensitivity in their ability to detect postural abnormalities. Postural sway is quantified, and a greater degree of sway is indicative of poorer postural control. Furthermore, these instrumental measures also allow researchers to manipulate the placement of the feet, and whether or not participants complete the task with their eyes opened or closed. Marvel and colleagues (64) were the first to use such a measure of balance to investigate postural control in patients with schizophrenia. This investigation demonstrated that patients with schizophrenia have deficits in postural control such that they sway more than controls, though they did not see any further effects of alcohol use (64). These findings were recently replicated by Kent and colleagues (65), and they demonstrated that in patients, greater postural sway was associated with worse general psychopathology symptoms. There was a similar trend with respect to negative symptoms (such as anhedonia). Importantly, in both of these investigations anti-psychotic medications do not seem to be impacting the findings (64, 65). The findings of increased sway were also replicated across a heterogeneous group of patients with psychosis, including those with schizophrenia, acute psychosis, and undefined psychotic disorder (66). It is of note, however, that an additional recent study is not consistent with these findings (67).

To our knowledge, there has been only one study investigating postural control in UHR individuals. We recently investigated whether or not adolescents and young adults at UHR for psychosis show impaired postural control as measured by increased sway area (1). We found that postural control deficits are indeed present in UHR individuals. Furthermore, greater sway area was associated with increased negative symptoms. Finally, we investigated cerebello-cortical networks using resting state connectivity MRI. Not only were cerebello-cortical networks weaker in the UHR group relative to the controls, but they were also correlated with postural sway, providing a link between cerebellar networks and behavior in this population (1).

Future directions regarding postural control across the psychosis spectrum fall into several key domains. First is the use of instrumental measures to quantify postural sway. Since Marvel and colleagues first used this method in patients with schizophrenia (64) there have been several replications. Using such methods whenever possible provides a more sensitive measure of postural control, and also allows for better comparison across investigations. Relatedly, such methods also lend themselves to more complex statistical analysis techniques, which may yield additional important information regarding postural control and schizophrenia, as demonstrated by Kent and colleagues (65). Second, additional investigations and replications of our recent findings regarding postural control deficits in UHR populations (1) are warranted. Follow-ups across disease progression in longitudinal investigations will also be especially informative. Finally, more direct links with cerebellar structure and function in patient groups are needed. While there is strong evidence in healthy individuals and in other clinical populations linking the cerebellum more directly to cerebellar structure and function (57, 58, 63), such work is lacking across the psychosis spectrum.

TIMING

The cerebellum has been implicated in timing function across multiple research domains. Assessments in cerebellar patients have indicated that these individuals are impaired in both timing production and perception (68), and more recently, these impairments have been linked more specifically to discontinuous timing tasks, such as discrete finger tapping (69). Furthermore, functional neuroimaging methods have also implicated the cerebellum in timing perception (70, 71). Overall, the cerebellum is thought to be generally very important in timing, particularly with respect to precise event timing (72). It has been suggested that the cerebellum is particularly important in timing on the sub-second scale, and that longer timing intervals (supra-second) are more cognitively mediated, and may be related to the basal ganglia (72). On the whole the cerebellum is certainly implicated in timing and this is important for a wide array of motor tasks such as finger tapping and sequence learning. With respect to schizophrenia, there is evidence to indicate that timing functions, particularly those that are purported to be cerebellar-dependent are impaired. Here, we will focus primarily on sub-second timing, as this is most closely linked to the cerebellum.

Before discussing the timing deficits seen in patients with schizophrenia, it is important to understand the more common methods to investigate timing. Broadly speaking, these paradigms fall into two categories – time perception and production. The most typical way of assessing time perception is with a temporal

bisection task. During a temporal bisection task, participants are presented with anchor durations that are either long or short. Then, test durations are presented and participants are asked to determine if the test duration is closer to the long or short anchor, and timing variability and temporal precision can be quantified [e.g., (48)]. Production tasks typically involved finger tapping using a synchronization–continuation type paradigm. Participants synchronize their tapping to a tone, and the tone is then taken away while tapping continues. Tap variability, often measured as the coefficient of variation, is used to quantify timing in these paradigms [e.g., (49)]. In both cases, the intervals used can vary to include both sub- and supra-second timing.

While investigations of timing in schizophrenia are certainly nothing new, earlier work largely focused on intervals of several seconds [e.g., Ref. (50–52)], which are thought to be more cognitively demanding, and are less likely to involve the cerebellum. More recent work, however, has investigated these sub-second durations in schizophrenia. The first of these investigations was by Elvevåg and colleagues (73). This study included two tasks, a temporal bisection task, as well as a temporal generalization task where participants had to recognize a standard duration. Across both domains, patients with schizophrenia were impaired with respect to controls, and importantly, performance was not correlated with working memory abilities, nor was it strongly associated with general intelligence (73). Davalos and colleagues replicated these findings even when the time between the anchor and test durations was varied (74), and similar results are seen with stimuli in both the auditory and visual domains (75). The patient group was impaired in both domains, but the impairment was greatest for the auditory presentation of stimuli. Interestingly, deficits have also been seen in patients with schizophrenia that have first-rank symptoms (76). These individuals experience hallucinations and thoughts that they believe to be under the control of another agent. The authors suggest that these patients may have a slowed internal pacemaker such that they experience time differently. However, it is crucial to note that these differences were not present in patients without first-rank symptoms (76), though it is possible that such sub-groups may be driving the effects in other investigations.

As noted above, sub-second intervals are thought to be more reliant upon the cerebellum, while supra-second intervals rely upon other neural systems, perhaps the basal ganglia, and are postulated to be more cognitively demanding (72). While the primary focus here is on cerebellar-mediated motor behaviors, work by Carroll and colleagues comparing temporal bisection performance on sub- and supra-second durations is worth noting (77). In this investigation, the patients were impaired in both timing ranges and the authors suggest that this may be indicative of a more general timing deficit in schizophrenia (77). There were also no associations with time deficits and symptomatology. However, it is worth noting that the sub-second findings not only support the cerebellar deficits in schizophrenia, the basal ganglia, and prefrontal cortex, which are important for more cognitively mediated tasks, have long since been implicated in schizophrenia (78). Thus, the longer supra-second durations may be tapping into additional neural systems that are impacted by the disease.

The majority of timing work has been done using time perception. In the one study, we know of using a synchronization–continuation time production task, there are also deficits in patients with schizophrenia as compared to controls during both the synchronization and continuation phases (79). During this task, tapping variability was increased in patients during both task phases. Furthermore, models of timing indicated that in patients with schizophrenia the deficit was due to actual deficits in timing as opposed to task performance or implementation (79). The motor production aspects of timing production may also come into play in motor learning tasks that involve timed, sequential finger movements (please see below).

Across the psychosis spectrum and in UHR individuals there has been very little work to date on timing. In those at genetic risk, a timing deficit was found, but this study was limited to supra-second durations, and similar supra-second deficits are seen in those with high schizotypy based on the Schizotypal Personality Questionnaire (80, 81). Thus, investigations of sub-second cerebellar-mediated timing tasks are necessary in UHR populations. However, sub- and supra-second performance was correlated with schizotypy dimensions (81). Overall, it is clear that further work is needed in these populations to better understand cerebellar-mediated timing deficits.

Future directions with respect to timing deficits fall into several domains. Most importantly is the need for additional work using temporal production tasks at the sub-second level in patients with schizophrenia. Relatedly, there is a general lack of research on this domain in at-risk populations and across the psychosis spectrum. Understanding whether or not such sub-second timing deficits exist prior to the onset of formal psychosis will provide us important insight as to the range of cerebellar-motor dysfunction prior to disease. Next, translation of such tasks to the scanner environment using functional neuroimaging is warranted, as are investigations looking at associations with regional cerebellar volume. While studies in individuals with cerebellar damage (69) and those using functional neuroimaging (70, 71) have implicated the cerebellum, such measures in schizophrenia and across the psychosis spectrum will further our understanding of the nature of this timing deficit in patients. Similarly, insightful relationships with regional cerebellar volume may be gleaned, and indeed Ivry and Spencer have suggested that there may be regional contributions of the cerebellum to timing (72). Finally, more work looking at timing with respect to symptom severity is needed.

MOTOR LEARNING

Motor learning is the process by which individuals learn to use new tools or devices, and turn novel and perhaps disjointed movements into fluid performance. Examples include learning to use a new computer mouse, or putting together a sequence of movements to shoot a basketball. The process of motor learning recruits a variety of cortical and subcortical brain regions (82–87), including the cerebellum. While it is certainly not the case that the cerebellum is engaged alone in motor learning, it does seem to be a key contributor, and investigating motor learning in patients with schizophrenia and those at UHR may be especially informative for our understanding of cerebellar–motor dysfunction in psychosis.

There are several different motor learning paradigms that are most typically used, and they seem to engage slightly different regions of the cerebellum (88). Motor sequence learning typically

requires participants to learn a new sequence of finger movements, and both accuracy and reaction time are compared to a random sequence of button presses. This can be done explicitly where the participant knows they are learning a sequence, or implicitly when a sequence is learned while the participant is unaware. Mirror-drawing is a form of implicit motor learning that requires participants to update their movements based on a mirror-reflection of their movements. Over multiple trials, participants are able to accurately trace complex shapes. Pursuit rotor tasks, which are also implicit, ask participants to track a target across a track pad using a mouse or joystick. The target is titrated so that the target moves with varying speed in order to ensure a standard minimum level of accuracy and time on target is calculated. Over several trials, the time on target increases, indicative of learning.

Early work investigating motor learning in schizophrenia was behavioral in nature. Deficits on a pursuit rotor task were demonstrated by Schwartz and colleagues (89). Patients with schizophrenia spent less time on the target and deficits were exacerbated by advanced age. Furthermore, these findings were not associated with medication or other movement abnormalities in the patient group, though they were weakly related to cognitive abilities. Using an implicit sequence learning task (serial reaction time task), Green and colleagues investigated motor learning in patients with schizophrenia (90). While both patients with schizophrenia and healthy controls showed overall improvement in reaction time over the course of the task, the patient group showed less learning. The authors suggested that this may be due to possible cerebellar deficits (90). Looking at both implicit and explicit sequence learning, Pederesen and colleagues found deficits in both domains relative to controls in those with first-episode schizophrenia (91). Using mirror-drawing paradigms, patients with schizophrenia have been shown to have implicit learning adaptation deficits (92–94). However, these deficits are often linked to medications in these patients.

These initial behavioral findings were soon followed up by neuroimaging investigations using functional, anatomical, structural, and connectivity methods (95–100). Though the measures of motor learning varied to some degree, with one exception (100), the behavioral findings were consistent with prior work indicating deficits in motor learning in patients with schizophrenia. In addition, these neuroimaging investigations also provide further information about what underlying brain differences may be contributing to these deficits.

Kumari and colleagues (95) showed that there are differential brain activations when comparing patients to controls, and this included both the cerebellum and regions in the basal ganglia. The patients with schizophrenia did not activate these regions, though they were activated by controls (95). The implication of the cerebellum is perhaps not surprising, and interesting given the proposed role of the cerebellum in schizophrenia. Implicit sequence learning has also been investigated in patients with schizophrenia using PET (96). The patients showed less learning over time when compared to the control participants. In the patient group, the pre-frontal cortex and cerebellum showed differential correlations with sequence learning, highlighting the importance of the cerebellum, but also the importance of investigating the interactions between the cerebellum and pre-frontal cortex. Null findings with regards to learning and the cerebellum in schizophrenia have also been reported (100). Recently, using meta-analysis, we investigated cerebellar functional activation across a variety of task domains including motor function (27). The majority of included motor studies related to finger tapping and motor sequence learning. While we cannot speak to performance in our analyses, across these studies we did find that in patients with schizophrenia cerebellar functional activation was altered relative to controls during motor tasks, indicating that perhaps patients with schizophrenia rely upon less efficient cerebellar networks and processing (27).

As noted above with respect to the findings of Marvel and colleagues (96) investigating the interactions between the cerebellum and cortex is potentially of great interest. One way to do so is with functional connectivity analyses. These analyses measure the correlations between the brain signal in different brain regions. Recently, Kasparek and colleagues (97) investigated motor sequencing abnormalities with respect to functional connectivity between the cerebellum and cortex assessed while subjects were making finger movements (finger-to-thumb opposition). Motor sequencing was indexed based on the Neurological Evaluation Scale (NES). Both patients and controls were assessed and then divided into those with sequencing abnormalities and those without, regardless of diagnosis. However, motor sequencing deficits were more common in the patient group. There were no differences between patients with schizophrenia and controls with respect to functional connectivity; but, those with motor sequencing deficits had lower functional connectivity between the cerebellum and the motor cortex (101). Though the differences were not related to diagnosis, given that motor sequencing deficits were more common in the patient group, this finding is potentially important for understanding motor learning deficits in schizophrenia, and further highlights the role of the cerebellum.

Also relying upon the NES measure of sequencing, Hüttlova and colleagues recently looked at structural connectivity of the cerebellum using diffusion tensor imaging (DTI) (98). In the patients with motor sequencing deficits, there was decreased white matter structural integrity relative to controls in the superior cerebellar peduncle, which is the primary cerebellar efferent to the thalamus, whereas in the patients without deficits, differences relative to controls were seen in the corticospinal tract. This suggests potential sub-groups within schizophrenia related to motor sequencing, but also further highlights the cerebellum in motor deficits in this patient population.

Finally, structural MRI has been used with respect to sequence learning in patients with schizophrenia (99). Volumes of the cerebellum and pre-supplementary motor area (SMA) were investigated. First, the only group differences in volume were seen in the pre-SMA, and in patients volume in this region was correlated with implicit learning. While it is notable that there were no group differences in total cerebellar volume, nor were there any cerebellar-behavior relationships, the measurement of the entire structure may be a contributing factor. In sum, across multiple studies, there seem to be relatively robust deficits in motor sequence learning and in procedural learning in patients with schizophrenia, and

this is supported by meta-analysis (102). Furthermore, there is at this point at least some evidence linking these deficits to the cerebellum, along with other liable neural substrates.

Though there has been a good deal of investigation related to motor learning in patients with schizophrenia, across the psychosis spectrum this has been investigated less extensively. In schizotypal individuals relative to controls, there do not appear to be any deficits in motor sequence learning, as measured using the implicit serial reaction time task (103, 104). However, more recently, we demonstrated procedural learning deficits in UHR patients relative to controls using a pursuit rotor task (2). Furthermore, learning was associated with volume of Crus I of the cerebellum. Given the cognitive functions of this region (4), and its associations with the pre-frontal cortex (105), this is an especially interesting finding, and may perhaps be related to the differing relationships with learning seen in the pre-frontal cortex and cerebellum (96). This may be due in part to the overall difficulty of this task as more complex motor tasks recruit this region of the cerebellum (106), though we may also be tapping into cognitive deficits as well.

Future directions in motor learning research across the psychosis spectrum include the further investigation of motor learning in psychosis spectrum populations. While there have been some inroads in this domain, further research is clearly warranted. Additionally, interesting investigations using non-invasive brain stimulation to the cerebellum have been completed in healthy individuals (107, 108). This stimulation can influence motor learning in these healthy individuals, and the impact on motor learning in patients with schizophrenia or across the psychosis spectrum may be especially informative. Finally, while there has been a great deal of work looking at the functional MRI correlates of motor learning in patients with schizophrenia, inclusion of anatomical and structural connectivity measures will be especially informative, both with respect to cerebellar pathology, but also to other brain regions implicated in motor learning.

Importantly, across all of these domains medication and cognitive deficits may be impacting performance. For example, deficits in mirror-drawing seem to be largely tied to medication (92–94), and our recent findings with respect to the cerebellum and pursuit rotor implicate cognitive cerebellar regions (2). Findings of cerebellar–motor deficits in at-risk populations where anti-psychotics are less commonly used indicate that many of these deficits are not an artifact of medications. However, not all studies of at-risk groups include only anti-psychotic naïve participants, and in patient groups, medications may be exacerbating these findings. Similarly, cognitive deficits in patients with schizophrenia may also be confounding these motor findings as motor performance is certainly closely linked to cognitive function [e.g., Ref. (109, 110)].

Finally, as noted throughout, and with the exception of motor learning, across most domains evidence directly linking these motor behaviors to the cerebellum are generally lacking. As such, the implication of cerebellar dysfunction is relatively indirect. By combining these motor measures with neuroimaging techniques we can better investigate the cerebellum in psychosis. Importantly, by combining these behavioral measures with measures of cerebellar volume or function, we can more effectively establish whether or not these behaviors may serve as markers of disease, and in clinical high-risk populations, they may serve as predictive biomarkers, as recently suggested by Bolbecker and colleagues (52). However, the cerebellum is a relatively large structure that is involved in both motor and non-motor behaviors (34, 35). An understanding of the cerebellar functional topography (4, 111) is important when considering the structure and its role in disease. It is important to consider the regional and functional organization within the cerebellum when looking to link the structure to overt motor deficits seen across the psychosis spectrum.

CEREBELLAR FUNCTIONAL TOPOGRAPHY

Beginning in the mid 1980s, investigators began speculating about the non-motor role of the cerebellum (28–31, 112). Investigations in non-human primates provided additional support for this notion. Using viral tract tracing methods, distinct tracts connecting pre-frontal and primary motor regions of the cortex to the cerebellum were revealed (113–116). These closed-loop circuits provide topographically segregated connections with the cerebral cortex. Specifically, the anterior aspects of the cerebellum (largely lobule V, but also lobules IV, and VI) along with a region in the inferior posterior cerebellum (lobules VIIIa and VIIIb) were connected to the primary motor cortex. Conversely, lateral aspects of the cerebellum (Crus II) were connected to the pre-frontal cortex (113). Similar motor and pre-frontal dissociations were seen in the dorsal and ventral aspects, respectively, of the cerebellar dentate nucleus (115).

More recently, using both structural (DTI) and functional connectivity neuroimaging (fcMRI) methods, a parallel topography of connections has been demonstrated in the human brain as well. fcMRI has revealed comparable distinct motor and cognitive networks in the cerebellar hemispheres at rest, based on the correlation between the resting state brain signal in these regions (117–119), and the dorsal and ventral dentate distinction was also replicated in humans using this methodology (120). However, distinct cerebello-cortical networks go beyond just a general motor/pre-frontal (non-motor) distinction. By investigating the resting state cerebello-cortical networks of individual cerebellar lobules, Bernard and colleagues showed that on a lobular level, the cerebellum is uniquely coupled with distinct cortical regions, resulting in distinct networks (105). Further support for multiple distinct motor and non-motor cerebellar networks comes from the work of Buckner and colleagues (121) (**Figure 1A**). They created a cerebellar parcelation based on coupling with multiple cortical resting state networks of the cortex. Finally, DTI has demonstrated distinct white matter tracts connecting the cerebellum and the cortex, that nicely parallel non-human primate literature (122). Thus, the cerebellum has distinct motor and non-motor closed-loop circuits with the cerebral cortex.

While the dissociable structural and functional motor and non-motor connections between the cerebellum and the cerebral cortex provide evidence for a topographically distinct functional organization in the cerebellum, there is also additional evidence from lesion studies and functional neuroimaging. The notion of a cognitive affective syndrome due to damage in the posterior lobe of the cerebellum was initially described by Schmahmann and Sherman (31). More recently, several investigations by Stoodley and colleagues (4, 111, 124) using both meta-analysis and functional

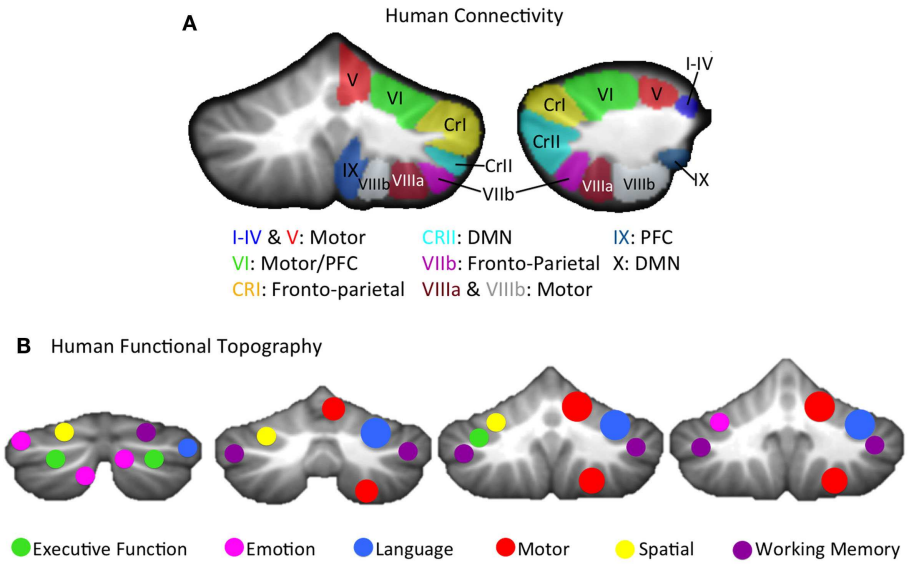


FIGURE 1 | (A) A lobular summary of resting state connectivity (left: coronal, right: sagittal) analyses conducted in humans, shown for the right cerebellar hemisphere, and concatenated across several studies (105, 121). Lobules of the right hemisphere are labeled, and general connectivity patterns are listed. The cerebellar vermis, made up of mid-line lobular aspects analogous to the hemispheres was not included, but distinct connectivity patterns, comparable to those seen in their hemispheric counterparts, have been reported (105). **(B)** A summary of the cerebellar functional topography presented on coronal slices (left to right, posterior to anterior), as demonstrated in humans using meta-analysis (4, 123) as well as functional neuroimaging (111) is provided. Verbal and spatial processing is differentially lateralized, and motor and non-motor processing patterns are relatively consistent with cerebellar sub-regions that are associated with motor and non-motor cortical regions, respectively. Motor activation was largely localized to the right hemisphere, given that only right handed individuals were included in these investigations. CRI, Crus I; CRII, Crus II; DMN, default mode network; PFC, pre-frontal cortex.

neuroimaging indicate that in addition to the closed-loop circuitry of the cerebellum, there is also a distinct topography of functional activation across different task domains (**Figure 1B**). That is, tasks such as working memory and motor tapping result in activations in distinct cerebellar regions. Likewise, language and spatial processing are lateralized as in the cortex (4, 111), and there is some evidence of a unique area active when processing emotion (4). Even within the anterior cerebellum, there appear to be sub-regions associated with distinct types of motor behavior and learning (88). Finally, in healthy individuals, regional cerebellar volume is also associated with individual differences in behavioral performance on motor and cognitive tasks in regionally specific ways (58). Importantly, there is increasing evidence to indicate that the cerebellum is processing non-motor information in many of these higher order cognitive tasks (125), and that cerebellar contributions are necessary for effective task performance, and not just an artifact of the structure's connections with the cerebral cortex (33). Given the diverse functional contributions of the cerebellum and the topographical nature of the activation associated with these task domains, the potential benefits of more targeted regional investigations are clear. Distinct cortico-cerebellar circuits and cerebellar regions may be differentially impacted in the disease state, and consideration of this putative regional variability may provide additional clarity for our understanding of the cerebellum in psychosis. Not only might this provide key insights into the motor deficits seen in schizophrenia and psychosis-risk, but it may also shed light on the various cognitive deficits that accompany the disorder.

REGIONAL CEREBELLAR INVESTIGATIONS

Converging evidence indicates that there are distinct functional sub-regions within the cerebellum making up a functional topography within the structure. Furthermore, the sub-regions of the cerebellum are part of distinct motor and non-motor cortical circuits. As such, when investigating the cerebellum it is important to consider the structure regionally. Making up approximately 10% of the total brain volume, the cerebellum is especially large to be considered as a whole. Its size, coupled with the known functional sub-regions call for a more fine-grained approach. It may be that sub-regions of the cerebellum are differentially impacted in the disease state. Not only would this approach provide important insight into the cerebellum across the psychosis spectrum, but it would also allow for comparisons across psychopathology. Cerebellar morphological differences with respect to controls have been observed in both depression and bipolar disorder (126–129). Understanding whether or not individual sub-regions or lobules are impacted differently across disease types will increase our understanding of the cerebellar contributions to psychopathology.

Post-mortem investigations provided some of the first evidence to indicate that there are cerebellar morphological differences in patients with schizophrenia with respect to controls. Differences when compared to controls have indicated reduced gyrification in the cerebellar vermis in patients (130), decreased neuronal integrity in patients, also in the cerebellar vermis (131), and there is a decrease in Purkinje cell (one of the main cerebellar cell types) density (fewer Purkinje cells) in patients with schizophrenia, as compared to controls (132). However, these results have

been somewhat mixed with some groups showing no differences in patients relative to controls (133–135). These mixed findings may be because cerebellar deficits are specific to certain subtypes of schizophrenia as suggested by Lohr and colleagues (133), though regional sampling (or lack thereof) may also come into play in these investigations. Despite the mixed results, this work has provided important insights into the cerebellum in schizophrenia, particularly with respect to the underlying cytoarchitectonic pathology. That is, any possible volumetric differences seen using neuroimaging may be due to the decreased neuronal integrity and smaller number of Purkinje cells revealed in these post-mortem investigations. However, one weakness in this method is the fact that in at-risk populations (both genetic and UHR), there is a lack of post-mortem data as these individuals are typically quite young. Thus, we can only make inferences regarding cerebellar cytoarchitecture in these populations, and are reliant upon neuroimaging research.

Thanks to *in vivo* neuroimaging methods, there is increasing evidence to indicate that there are morphological differences in the cerebella of patients with schizophrenia, and there is an emerging literature indicating this in psychosis-risk as well (both UHR and genetic). However, the results thus far are relatively mixed [for a review, see Ref. (28)]. That is, in some cases, patients with schizophrenia have larger cerebellar volumes than controls, whereas in other cases, cerebellar volume in patients is decreased with respect to controls [cf. (28)]. Subsequent to the review of Shenton and colleagues, additional mixed findings with respect to cerebellar volume in schizophrenia have been revealed (136–142). The majority of these studies were methodologically similar in that they looked at the cerebellar hemispheres as a whole, and also investigated the vermis, which was often further subdivided into vermal sub-regions. The most consistent differences were found in the vermis across studies (136, 140), and the more detailed approach taken to investigating the vermis may be a contributing factor. The literature on the cerebellum in those at-risk for psychosis (UHR and genetic risk) is much smaller than that in schizophrenia, but the mixed findings persist (2, 142–144). However, they did differ methodologically, largely relying upon whole brain methods to assess gray matter. While this is not an exhaustive list of investigations of the cerebellum in schizophrenia and psychosis-risk, it is clear that the results are mixed, and while differences in study inclusion factors and subject age may contribute, we suggest that the gross measures of cerebellar volume, particularly in the hemispheres are a contributing factor.

Assessments of the cerebellum taking regional approaches are certainly the exception to the rule, and the few cases where these approaches have been used have provided interesting results. In a relatively small sample ($n = 19$), Loeher and colleagues (141) traced individual cerebellar lobules and found volumetric differences in the vermis. In childhood-onset schizophrenia, siblings, and healthy controls, Greenstein and colleagues also investigated cerebellar sub-regions (142). Though they did not look at individual lobules, they did subdivide the cerebellar hemispheres based on anatomical boundaries, providing increased detail relative to whole hemisphere analyses. In this study, the patients with schizophrenia ($n = 94$) had smaller anterior cerebellar volume, as well as smaller vermis volume when compared to controls, and they also showed differing developmental volumetric trajectories with respect to controls. Though the siblings of the patients did not differ in their regional cerebellar volumes from controls at baseline, they did show differing regional volumetric trajectories during longitudinal assessments (142). The detailed approaches taken here, along with the large sample size provide important insights with respect to cerebellar volume across the schizophrenia spectrum, and indicate that cerebellar sub-regions may be differentially impacted. As discussed above, Edwards and colleagues (43) investigated the anterior and posterior cerebellum with respect to eyeblink conditioning. They found smaller anterior cerebellar volume in patients with schizophrenia, and though there were no significant correlations with behavior in the patient group, the relationships were in the opposite direction as compared to controls. The authors as a result suggested that there may be altered structure–function relationships in schizophrenia with respect to the cerebellum and eye-blink conditioning (43). Using automatic lobular segmentation methods (58) we recently demonstrated that there are regional lobular differences in UHR adolescents and young adults (2). The anterior cerebellum and Crus I differed between the patient group and age-matched healthy controls, as did the vermis, though lobule X did not differ. Though this study was focused on specific cerebellar lobules, this provides further preliminary evidence that regional cerebellar volumetric differences may be present prior to the development of psychosis, and as we continue to longitudinally investigate these individuals, we will be able to investigate their volumetric trajectories over time. Finally, an intriguing new study looking at modularity of the cerebellum using DTI, indicates that the modular organization of the cerebellum is altered in schizophrenia (145). This finding further underscores the importance of regional approaches, as the functional architecture of the cerebellum seems to differ in schizophrenia (93), and these structural findings may underlie this (145).

It is clear that cerebellar-mediated motor behaviors are impacted in patients with schizophrenia, and across the psychosis spectrum. There are also cognitive deficits that may be linked, at least in part, to the cerebellum. From a morphological or network perspective, the contributions of the cerebellum are better understood by investigating this structure regionally. This may provide key insights into both the motor and cognitive deficits experienced by patients with schizophrenia and psychosis-risk groups. In the work summarized above, though the cerebellum is implicated in these motor deficits, direct links between morphology and performance are generally lacking. By taking a regional approach, specific hypotheses with respect to the cerebellum and motor performance can be defined and tested to better understand cerebellar-motor deficits across the psychosis spectrum. Applying this approach to procedural learning in UHR populations, we demonstrated that volume of Crus I in at-risk individuals was positively correlated with procedural learning (2). Interestingly, this motor task was associated with a more cognitive region of the cerebellum, suggesting that cognitive circuits, which are implicated in complex motor tasks (106) are perhaps also implicated in the cerebellar-motor deficits seen across the psychosis spectrum. Future investigations including regional measures of cerebellar volume with respect to motor deficits are warranted, and will likely provide important insights into the involvement of this structure in the disease state.

Most importantly, it is now much easier to investigate the cerebellum, especially morphology, on a lobular basis. While in the

past such detailed analyses would require precise hand tracing of individual cerebellar lobules requiring large amounts of time and multiple raters, several recent studies have presented automatic lobular segmentation methods (58, 146, 147). These methods allow for investigators to easily compute lobular cerebellar volumes, and can be applied to large clinical samples, eliminating much of the methodological challenge associated with hand tracing. Bernard and Seidler (58) used the lobular delineations and masks originally created by Diedrichsen and colleagues as part of the SUIT atlas (148, 149). We successfully applied these methods in an investigation of adolescents and healthy controls at ultra-high risk for psychosis (2), demonstrating their utility in clinical populations, and providing important information about both regional cerebellar volume as well as motor learning in this population. Similarly, the lobular delineations available in the SUIT atlas can be used as starting seed regions for resting state connectivity analyses (1, 105, 150), and such analyses have revealed interesting differences and associations between lobular cerebellar connectivity, postural control, and symptom severity in UHR individuals (1). Finally, these regions may also serve as useful starting points for DTI analyses. Salmi and colleagues looked at cerebello-thalamo-cortical white matter networks in healthy adults (122), and similar analyses across the psychosis spectrum would be beneficial to our understanding of the role of the cerebellum in motor deficits, as well with respect to the disease state more generally.

CONCLUSION

A range of cerebellar-mediated motor tasks are impacted across the psychosis spectrum. Such motor impairments are present prior to disease onset, and may serve as a marker for pre-morbid cerebellar dysfunction. However, to date, direct links between these motor impairments and cerebellar morphology and/or cerebello-cortical networks have generally been lacking. In part, this may be due to standard approaches that treat the cerebellum as a functionally homogenous brain structure, though converging evidence indicates that there are distinct motor and non-motor functional regions within the cerebellum [e.g., Ref. (16, 23, 34, 90)]. Thus, we suggest that more specific topographically informed approaches to investigating the cerebellum (particularly with respect to cerebellar morphology and cerebello-cortical networks) across the psychosis spectrum will yield informative results with respect to the involvement of the cerebellum in psychosis. Such analyses will provide important information with respect to motor dysfunction, and they also may shed light on mixed findings with respect to cerebellar morphology. Furthermore, such an approach may provide additional insights into cognitive deficits experienced by these patient groups. That is, regional volume or functional differences may be limited to sub-regions of the cerebellum, and investigations of the structure as a whole may have masked these important findings. A better understanding of regional cerebellar morphological and functional differences will indicate whether or not there are more global or local cerebellar deficits in psychosis. Cerebellar-mediated movement abnormalities may be an overt manifestation of a more general cerebellar deficit, and regional analyses will allow this to be tested more directly. However, it is of note that these insights will be on a macro-structural level and potential underlying cellular differences and cellular contributions to pathophysiology are not assessed with these volumetric techniques. Computational models with respect of cerebellar cytoarchitectonics may be especially informative in that domain. Finally, regional approaches to investigating the cerebellum and cerebellar-motor abnormalities across disorders will allow for important comparisons resulting in a better understanding of the cerebellum across disorders.

ACKNOWLEDGMENTS

This work was supported by the National Institutes of Health (R01MH094650 to Vijay A. Mittal and F32MH102989-01 to Jessica A. Bernard). Publication of this article was funded by the University of Colorado Boulder Libraries Open Access Fund.

REFERENCES

1. Bernard JA, Dean DJ, Kent JS, Orr JM, Pelletier-Baldelli A, Lunsford-Avery J, et al. Cerebellar networks in individuals at ultra high-risk of psychosis: impact on postural sway and symptom severity. *Hum Brain Mapp* (2014) **35**:4064–78. doi:10.1002/hbm.22458
2. Dean DJ, Bernard JA, Orr JM, Pelletier-Baldelli A, Gupta T, Carol EE, et al. Cerebellar morphology and procedural learning impairment in neuroleptic-naive youth at ultrahigh risk of psychosis. *Clin Psychol Sci* (2013) **2**:152–64. doi:10.1177/2167702613500039
3. Mittal VA, Dean DJ, Bernard JA, Orr JM, Pelletier-Baldelli A, Carol EE, et al. Neurological soft signs predict abnormal cerebellar-thalamic tract development and negative symptoms in adolescents at high risk for psychosis: a longitudinal perspective. *Schizophr Bull* (2014) **40**:1204–15. doi:10.1093/schbul/sbt199
4. Stoodley CJ, Schmahmann JD. Functional topography in the human cerebellum: a meta-analysis of neuroimaging studies. *Neuroimage* (2009) **44**:489–501. doi:10.1016/j.neuroimage.2008.08.039
5. Andreasen NC, Olsen S. Negative v positive schizophrenia. *Arch Gen Psychiatry* (1982) **39**:789–94. doi:10.1001/archpsyc.1982.04290070025006
6. Mittal VA, Walker EF. Movement abnormalities: a putative biomarker of risk for psychosis. In: Ritsner MS, editor. *Neuropsychiatric Biomarkes, Endophenotypes, and Genes*. Springer Science + Business Media LLC (2009). p. 239–58.
7. Docx L, Morrens M, Bervoets C, Hulstijn W, Fransen E, De Hert M, et al. Parsing the components of the psychomotor syndrome in schizophrenia. *Acta Psychiatr Scand* (2012) **126**:256–65. doi:10.1111/j.1600-0447.2012.01846.x
8. Morrens M, Hulstijn W, Sabbe B. Psychomotor slowing in schizophrenia. *Schizophr Bull* (2007) **33**:1038–53. doi:10.1093/schbul/sbl051
9. Morrens M, Docx L, Walther S. Beyond boundaries: in search of an integrative view on motor symptoms in schizophrenia. *Front Psychiatry* (2014) **5**:145. doi:10.3389/fpsyt.2014.00145
10. Peralta V, Campos MS, De Jalón EG, Cuesta MJ. Motor behavior abnormalities in drug-naïve patients with schizophrenia spectrum disorders. *Mov Disord* (2010) **25**:1068–76. doi:10.1002/mds.23050
11. Pappa S, Dazzan P. Spontaneous movement disorders in antipsychotic-naive patients with first-episode psychoses: a systematic review. *Psychol Med* (2009) **39**:1065–76. doi:10.1017/S0033291708004716
12. Mittal VA, Daley M, Shiode MF, Bearden CE, O'Neill J, Cannon TD. Striatl volumes and dyskinetic movements in youth at high-risk for psychosis. *Schizophr Res* (2010) **123**:68–70. doi:10.1016/j.schres.2010.08.002.Striatal
13. Mittal VA, Dhruv S, Tessner KD, Walder DJ, Walker EF. The relations among putative biorisk markers in schizotypal adolescents: minor physical anomalies, movement abnormalities, and salivary cortisol. *Biol Psychiatry* (2007) **61**:1179–86. doi:10.1016/j.biopsych.2006.08.043
14. Mittal VA, Tessner KD, Trottman HD, Esterberg M, Dhrub SH, Simeonova DI, et al. Movement abnormalities and the progression of prodromal symptomatology in adolescents at risk for psychotic disorders. *J Abnorm Psychol* (2007) **116**:260–7. doi:10.1037/0021-843X.116.2.260
15. Mittal VA, Walker EF. Movement abnormalities predict conversion to axis I psychosis among prodromal adolescents. *J Abnorm Psychol* (2007) **116**:796–803. doi:10.1037/0021-843X.116.4.796
16. Mittal VA, Neumann C, Saczawa M, Walker EF. Longitudinal progression of movement abnormalities in relation to psychotic symptoms in adolescents at high risk of schizophrenia. *Arch Gen Psychiatry* (2008) **65**:165–71. doi:10.1001/archgenpsychiatry.2007.23

17. Mittal VA, Walker EF, Bearden CE, Walder D, Trottman H, Daley M, et al. Markers of basal ganglia dysfunction and conversion to psychosis: neurocognitive deficits and dyskinesias in the prodromal period. *Biol Psychiatry* (2010) **68**:93–9. doi:10.1016/j.biopsych.2010.01.021.Markers
18. Mittal VA, Walker EF. Movement abnormalities and schizophrenia in DSM-V. *Psychol Med* (2010) **40**:1581–3. doi:10.1017/S0033291710001352
19. Mittal VA, Jalbrzikowski M, Daley M, Roman C, Bearden CE, Cannon TD. Abnormal movements are associated with poor psychosocial functioning in adolescents at high risk for psychosis. *Schizophr Res* (2011) **130**:164–9. doi:10.1016/j.schres.2011.05.007
20. Mittal VA, Walker EF. Dyskinesias, tics, and psychosis: issues for the next diagnostic and statistical manual of mental disorders. *Psychiatry Res* (2013) **189**:158–9. doi:10.1016/j.psychres.2011.06.006.Dyskinesias
21. Dean DJ, Teulings H-L, Caligiuri M, Mittal VA. Handwriting analysis indicates spontaneous dyskinesias in neuroleptic naïve adolescents at high risk for psychosis. *J Vis Exp* (2014) **81**:e50852. doi:10.3791/50852.Handwriting
22. Mittal VA, Orr JM, Turner J, Pelletier AL, Dean DJ, Lunsford-Avery J, et al. Striatal abnormalities and spontaneous dyskinesias in non-clinical psychosis. *Schizophr Res* (2013) **151**:141–7. doi:10.1016/j.schres.2013.10.003
23. Andreasen NC, O'Leary DS, Cizadlo T, Arndt S, Rezai K, Ponto LL, et al. Schizophrenia and cognitive dysmetria: a positron-emission tomography study of dysfunctional prefrontal-thalamic-cerebellar circuitry. *Proc Natl Acad Sci U S A* (1996) **93**:9985–90. doi:10.1073/pnas.93.18.9985
24. Andreasen NC, Paradiso S, O'Leary DS. "Cognitive dysmetria" as an integrative theory of schizophrenia: a dysfunction in cortical-subcortical-cerebellar circuitry? *Schizophr Bull* (1998) **24**:203–18. doi:10.1093/oxfordjournals.schbul.a033321
25. Picard H, Amado I, Mouchet-Mages S, Olié J-P, Krebs M-O. The role of the cerebellum in schizophrenia: an update of clinical, cognitive, and functional evidences. *Schizophr Bull* (2008) **34**:155–72. doi:10.1093/schbul/sbm049
26. Barch DM. Cerebellar-thalamic connectivity in schizophrenia. *Schizophr Bull* (2014) **40**:1200–3. doi:10.1093/schbul/sbu076
27. Bernard JA, Mittal VA. Dysfunctional activation of the cerebellum in schizophrenia: a functional neuroimaging meta-analysis. *Clin Psychol Sci* (2014). doi:10.1177/2167702614542463
28. Leiner HC, Leiner L, Dow RS. Reappraising the cerebellum: what does the hindbrain contribute to the forebrain? *Behav Neurosci* (1989) **103**:998–1008. doi:10.1037/0735-7044.103.5.998
29. Leiner HC, Leiner L, Dow RS. Cognitive and language functions of the human cerebellum. *Trends Neurosci* (1993) **16**:444–7. doi:10.1016/0166-2236(93)90072-T
30. Leiner HC, Leiner AL, Dow RS. Does the cerebellum contribute to mental skills? *Behav Neurosci* (1986) **100**:443–54. doi:10.1037/0735-7044.100.4.443
31. Schmahmann JD, Sherman JC. The cerebellar cognitive affective syndrome. *Brain* (1998) **121**(Pt 4):561–79. doi:10.1093/brain/121.4.561
32. Chen SHA, Desmond JE. Temporal dynamics of cerebro-cerebellar network recruitment during a cognitive task. *Neuropsychologia* (2005) **43**:1227–37. doi:10.1016/j.neuropsychologia.2004.12.015
33. Desmond JE, Chen SHA, Shieh PB. Cerebellar transcranial magnetic stimulation impairs verbal working memory. *Ann Neurol* (2005) **58**:553–60. doi:10.1002/ana.20604
34. Ramnani N. The primate cortico-cerebellar system: anatomy and function. *Nat Rev Neurosci* (2006) **7**:511–22. doi:10.1038/nrn1953
35. Ito M. Control of mental activities by internal models in the cerebellum. *Nat Rev Neurosci* (2008) **9**:304–13. doi:10.1038/nrn2332
36. Spencer RMC, Ivry RB. Cerebellum and timing. In: Manto M, Schmahmann JD, Rossi F, Gruol DL, Koibuchi N, editors. *Handbook of the Cerebellum and Cerebellar Disorders*. New York: Springer (2013). p. 1201–19.
37. Keele SW, Ivry RB. Does the cerebellum provide a common computation for diverse tasks? A timing hypothesis. *Ann N Y Acad Sci* (1990) **6-8**:179–211. doi:10.1111/j.1749-6632.1990.tb48897.x
38. Kim JJ, Thompson RF. Cerebellar circuits and synaptic mechanisms involved in classical eyeblink conditioning. *Trends Neurosci* (1997) **20**:177–81. doi:10.1016/S0166-2236(96)10081-3
39. Gerwig M, Kolb FP, Timmann D. The involvement of the human cerebellum in eyeblink conditioning. *Cerebellum* (2007) **6**:38–57. doi:10.1080/14734220701225904
40. Lindquist DH, Steinmetz JE, Thompson RF. Cerebellum and eyeblink conditioning. In: Manto M, Schmahmann JD, Rossi F, Gruol DL, Koibuchi N, editors. *Handbook of the Cerebellum and Cerebellar Disorders*. Dordrecht: Springer (2013). p. 1175–90.
41. Bolbecker AR, Mehta CS, Edwards CR, Steinmetz JE, O'Donnell BF, Hetrick WP. Eye-blink conditioning deficits indicate temporal processing abnormalities in schizophrenia. *Schizophr Res* (2009) **111**:182–91. doi:10.1016/j.schres.2009.03.016
42. Brown SM, Kieffaber PD, Carroll C, Vohs JL, Tracy J, Shekhar A, et al. Eyeblink conditioning deficits indicate timing and cerebellar abnormalities in schizophrenia. *Brain Cogn* (2005) **58**:94–108. doi:10.1016/j.bandc.2004.09.011
43. Edwards CR, Newman S, Bismark A, Skosnik PD, O'Donnell BF, Shekhar A, et al. Cerebellum volume and eyeblink conditioning in schizophrenia. *Psychiatry Res* (2008) **162**:185–94. doi:10.1016/j.pscychresns.2007.06.001
44. Bolbecker AR, Steinmetz AB, Mehta CS, Forsyth JK, Klaunig MJ, Lazar EK, et al. Exploration of cerebellar-dependent associative learning in schizophrenia: effects of varying and shifting interstimulus interval on eyeblink conditioning. *Behav Neurosci* (2011) **125**:687–98. doi:10.1037/a0025150
45. Forsyth JK, Bolbecker AR, Mehta CS, Klaunig MJ, Steinmetz JE, O'Donnell BF, et al. Cerebellar-dependent eyeblink conditioning deficits in schizophrenia spectrum disorders. *Schizophr Bull* (2012) **38**:751–9. doi:10.1093/schbul/sbq148
46. Parker KL, Andreasen NC, Liu D, Freeman JH, O'Leary DS. Eyeblink conditioning in unmedicated schizophrenia patients: a positron emission tomography study. *Psychiatry Res* (2013) **214**:402–9. doi:10.1016/j.pscychresns.2013.07.006
47. Coesmans M, Röder CH, Smit AE, Koekkoek SKE, de Zeeuw CI, Frens MA, et al. Cerebellar motor learning deficits in medicated and medication-free men with recent-onset schizophrenia. *J Psychiatry Neurosci* (2014) **39**:3–11. doi:10.1503/jpn.120205
48. Sears LL, Andreasen NC, O'Leary DS. Cerebellar functional abnormalities in schizophrenia are suggested by classical eyeblink conditioning. *Biol Psychiatry* (2000) **48**:204–9. doi:10.1016/S0006-3223(00)00247-X
49. Marenco S, Weinberger DR, Schreurs BG. Single-cue delay and trace classical conditioning in schizophrenia. *Biol Psychiatry* (2003) **53**:390–402. doi:10.1016/S0002-3223(03)01506-8
50. Stevens A, Schwarz J, Schwarz B, Ruf I, Kolter T, Czekalla J. Implicit and explicit learning in schizophrenics treated with olanzapine and with classic neuroleptics. *Psychopharmacology (Berl)* (2002) **160**:299–306. doi:10.1007/s00213-001-0974-1
51. Lubow RE. Classical eyeblink conditioning and schizophrenia: a short review. *Behav Brain Res* (2009) **202**:1–4. doi:10.1016/j.bbr.2009.03.006
52. Bolbecker AR, Kent JS, Petersen IT, Klaunig MJ, Forsyth JK, Howell JM, et al. Impaired cerebellar-dependent eyeblink conditioning in first-degree relatives of individuals with schizophrenia. *Schizophr Bull* (2014) **40**:1001–10. doi:10.1093/schbul/sbt112
53. Cheng DT, Disterhoft JF, Power JM, Ellis D, Desmond JE. Neural substrates underlying human delay and trace eyeblink conditioning. *Proc Natl Acad Sci U S A* (2008) **105**:8108–13. doi:10.1073/pnas.0800374105
54. Cheng DT, Meintjes EM, Stanton ME, Desmond JE, Pienaar M, Dodge NC, et al. Functional MRI of cerebellar activity during eyeblink classical conditioning in children and adults. *Hum Brain Mapp* (2014) **35**:1390–403. doi:10.1002/hbm.22261
55. Holmes G. The cerebellum of man. *Brain* (1939) **62**:1–30. doi:10.1093/brain/62.1.1
56. Diener HC, Dichgans J, Bacher M, Gompf B. Quantification of postural sway in normals and patients with cerebellar diseases. *Electroencephalogr Clin Neurophysiol* (1984) **57**:134–42. doi:10.1016/0013-4694(84)90172-X
57. Ouchi Y, Okada H, Yoshikawa E, Nobezawa S, Futatsubashi M. Brain activation during maintenance of standing postures in humans. *Brain* (1999) **122**:329–38. doi:10.1093/brain/122.2.329
58. Bernard JA, Seidler RD. Relationships between regional cerebellar volume and sensorimotor and cognitive function in young and older adults. *Cerebellum* (2013) **12**:721–37. doi:10.1007/s12311-013-0481-z
59. Sullivan EV, Rose J, Pfefferbaum A. Physiological and focal cerebellar substrates of abnormal postural sway and tremor in alcoholic women. *Biol Psychiatry* (2010) **67**:44–51. doi:10.1016/j.biopsych.2009.08.008
60. Sullivan EV, Rohlfing T, Pfefferbaum A. Pontocerebellar volume deficits and ataxia in alcoholic men and women: no evidence for "telescoping". *Psychopharmacology (Berl)* (2010) **208**:279–90. doi:10.1007/s00213-009-1729-7
61. Angyal A, Sherman MA. Postural reactions to vestibular stimulation in schizophrenic and normal subjects. *Am J Psychiatry* (1942) **98**:857–62.

62. Ho B-C, Mola C, Andreasen NC. Cerebellar dysfunction in neuroleptic naive schizophrenia patients: clinical, cognitive, and neuroanatomic correlates of cerebellar neurologic signs. *Biol Psychiatry* (2004) **55**:1146–53. doi:10.1016/j.biopsych.2004.02.020
63. Sullivan EV, Rosenbloom MJ, Pfefferbaum A. Balance and gait deficits in schizophrenia compounded by the comorbidity of alcoholism. *Am J Psychiatry* (2004) **161**:751–5. doi:10.1176/appi.ajp.161.4.751
64. Marvel CL, Schwartz BL, Rosse RB. A quantitative measure of postural sway deficits in schizophrenia. *Schizophr Res* (2004) **68**:363–72. doi:10.1016/j.schres.2003.09.003
65. Kent JS, Hong SL, Bolbecker AR, Klaunig MJ, Forsyth JK, O'Donnell BF, et al. Motor deficits in schizophrenia quantified by nonlinear analysis of postural sway. *PLoS One* (2012) **7**:e41808. doi:10.1371/journal.pone.0041808
66. Stensdotter A-K, Wanvik AK, Lorås HW. Postural control in quiet standing with a concurrent cognitive task in psychotic conditions. *J Mot Behav* (2013) **45**:279–87. doi:10.1080/00222895.2013.791241
67. Ahlgrén-Rimpiläinen A, Lauerma H, Kähkönen S, Aalto H, Pyykkö I, Palmgren K, et al. Effect of visual information on postural control in patients with schizophrenia. *J Nerv Ment Dis* (2010) **198**:601–3. doi:10.1097/NMD.0b013e3181ea16bc
68. Ivry RB, Keele SW. Timing functions of the cerebellum. *J Cogn Neurosci* (1989) **1**:136–52. doi:10.1162/jocn.1989.1.2.136
69. Spencer RMC, Zelaznik HN, Diedrichsen J, Ivry RB. Disrupted timing of discontinuous but not continuous movements by cerebellar lesions. *Science* (2003) **300**:1437–9. doi:10.1126/science.1083661
70. Jueptner M, Rijntjes M, Weiller C, Faiss JH, Timmann D, Mueller SP, et al. Localization of a cerebellar timing process using PET. *Neurology* (1995) **45**:1540–5. doi:10.1212/WNL.45.8.1540
71. Lewis P, Miall R. Brain activation patterns during measurement of sub- and supra-second intervals. *Neuropsychologia* (2003) **41**:1583–92. doi:10.1016/S0028-3932(03)00118-0
72. Ivry RB, Spencer RMC. The neural representation of time. *Curr Opin Neurobiol* (2004) **14**:225–32. doi:10.1016/j.conb.2004.03.013
73. Elvevåg B, McCormack T, Glibert A, Brown GDA, Wienberger DR, Goldberg TE. Duration judgements in patients with schizophrenia. *Psychol Med* (2003) **33**:1249–61. doi:10.1017/S0033291703008122
74. Davalos DB, Kisley M, Ross RG. Effects of interval duration on temporal processing in schizophrenia. *Brain Cogn* (2003) **52**:295–301. doi:10.1016/S0278-2626(03)00157-X
75. Carroll CA, Boggs J, O'Donnell BF, Shekhar A, Hetrick WP. Temporal processing dysfunction in schizophrenia. *Brain Cogn* (2008) **67**:150–61. doi:10.1016/j.bandc.2007.12.005
76. Waters F, Jablensky A. Time discrimination deficits in schizophrenia patients with first-rank (passivity) symptoms. *Psychiatry Res* (2009) **167**:12–20. doi:10.1016/j.psychres.2008.04.004
77. Carroll CA, O'Donnell BF, Shekhar A, Hetrick WP. Timing dysfunctions in schizophrenia span from millisecond to several-second durations. *Brain Cogn* (2009) **70**:181–90. doi:10.1016/j.bandc.2009.02.001
78. Buchsbaum MS. The frontal lobes, basal ganglia, and temporal lobes as sites for schizophrenia. *Schizophr Bull* (1990) **16**:379–89. doi:10.1093/schbul/16.3.379
79. Carroll CA, O'Donnell BF, Shekhar A, Hetrick WP. Timing dysfunctions in schizophrenia as measured by a repetitive finger tapping task. *Brain Cogn* (2009) **71**:345–53. doi:10.1016/j.bandc.2009.06.009
80. Penney TB, Meck WH, Roberts S, Gibbon J, Erlenmeyer-Kimling L. Interval-timing deficits in individuals at high risk for schizophrenia. *Brain Cogn* (2005) **58**:109–18. doi:10.1016/j.bandc.2004.09.012
81. Lee K-H, Dixon JK, Spence S, Woodruff PWR. Time perception dysfunction in psychometric schizotypy. *Pers Individ Dif* (2006) **40**:1363–73. doi:10.1016/j.paid.2005.10.021
82. Imamizu H, Miyauchi S, Tamada T, Sasaki Y, Takino R, Pütz B, et al. Human cerebellar activity reflecting an acquired internal model of a new tool. *Nature* (2000) **403**:192–5. doi:10.1038/35003194
83. Jenkins IH, Brooks DJ, Frackowiak RSJ, Passingham FE. Motor sequence tomography learning: a study with positron. *J Neurosci* (1994) **14**(6):3775–90.
84. Doyon J, Song AW, Karni A, Lalonde F, Adams MM, Ungerleider LG. Experience-dependent changes in cerebellar contributions to motor sequence learning. *Proc Natl Acad Sci U S A* (2002) **99**:1017–22. doi:10.1073/pnas.022615199
85. Doyon J, Benali H. Reorganization and plasticity in the adult brain during learning of motor skills. *Curr Opin Neurobiol* (2005) **15**:161–7. doi:10.1016/j.conb.2005.03.004
86. Seidler RD, Noll DC, Chintalapati P. Bilateral basal ganglia activation associated with sensorimotor adaptation. *Exp Brain Res* (2006) **175**:544–55. doi:10.1007/s00221-006-0571-y
87. Schendan HE, Searl MM, Melrose RJ, Stern CE. An FMRI study of the role of the medial temporal lobe in implicit and explicit sequence learning. *Neuron* (2003) **37**:1013–25. doi:10.1016/S0896-6273(03)00123-5
88. Bernard JA, Seidler RD. Cerebellar contributions to visuomotor adaptation and motor sequence learning: an ALE meta-analysis. *Front Hum Neurosci* (2013) **7**:27. doi:10.3389/fnhum.2013.00027
89. Schwartz BL, Rosse RB, Veazey C, Deutsch SI. Impaired motor skill learning in schizophrenia: implications for corticostriatal dysfunction. *Biol Psychiatry* (1996) **39**:241–8. doi:10.1016/0006-3223(95)00130-1
90. Green MF, Kern RS, Williams O, McGurk S, Kee K. Procedural learning in schizophrenia: evidence from serial reaction time. *Cogn Neuropsychiatry* (1997) **2**:123–34. doi:10.1080/135468097396360
91. Pedersen A, Siegmund A, Ohrmann P, Rist F, Rothermundt M, Suslow T, et al. Reduced implicit and explicit sequence learning in first-episode schizophrenia. *Neuropsychologia* (2008) **46**:186–95. doi:10.1016/j.neuropsychologia.2007.07.021
92. Bédard M-A, Scherer H, Delorimier J, Stip E, Lalonde P. Differential effects of D2-and D4-blocking neuroleptics on the procedural learning of schizophrenic patients. *Can J Psychiatry* (1996) **41**:S21–4.
93. Bédard M-A, Shérer H, Stip E, Cohen H, Rodriguez J-P, Richer F. Procedural learning in schizophrenia: further consideration on the deleterious effect of neuroleptics. *Brain Cogn* (2000) **43**:31–9.
94. Scherer H, Bedard M-A, Stip E, Paquet F, Richer F, Bériault M, et al. Procedural learning in schizophrenia can reflect the pharmacologic properties of the antipsychotic treatments. *Cogn Behav Neurol* (2004) **17**:32–40. doi:10.1097/00146965-200403000-00004
95. Kumari V, Gray J, Honey GD, Soni W, Bullmore ET, Williams SCR, et al. Procedural learning in schizophrenia: a functional magnetic resonance imaging investigation. *Schizophr Res* (2002) **57**:97–107. doi:10.1016/S0920-9964(01)00270-5
96. Marvel CL, Turner BM, O'Leary DS, Johnson HJ, Pierson RK, Ponto LLB, et al. The neural correlates of implicit sequence learning in schizophrenia. *Neuropsychology* (2007) **21**:761–77. doi:10.1037/0894-4105.21.6.761
97. Kasparek T, Rehulova J, Kerkovsky M, Sprlakova A, Mechl M, Mikl M. Corticocerebellar functional connectivity and sequencing of movements in schizophrenia. *BMC Psychiatry* (2012) **12**:17. doi:10.1186/1471-244X-12-17
98. Hüttlova J, Kikinis Z, Kerkovsky M, Bouix S, Vu M-A, Makris N, et al. Abnormalities in myelination of the superior cerebellar peduncle in patients with schizophrenia and deficits in movement sequencing. *Cerebellum* (2014) **13**:415–24. doi:10.1007/s12311-014-0550-y
99. Exner C, Weniger G, Schmidt-Samoa C, Irle E. Reduced size of the pre-supplementary motor cortex and impaired motor sequence learning in first-episode schizophrenia. *Schizophr Res* (2006) **84**:386–96. doi:10.1016/j.schres.2006.03.013
100. Zedkova L, Woodward ND, Harding I, Tibbo PG, Purdon SE. Procedural learning in schizophrenia investigated with functional magnetic resonance imaging. *Schizophr Res* (2006) **88**:198–207. doi:10.1016/j.schres.2006.06.039
101. Kasparek T, Prikryl R, Rehulova J, Marecek R, Mikl M, Prikrylova H, et al. Brain functional connectivity of male patients in remission after the first episode of schizophrenia. *Hum Brain Mapp* (2012) **34**(3):501–752. doi:10.1002/hbm.21469
102. Siegert RJ, Weatherall M, Bell EM. Is implicit sequence learning impaired in schizophrenia? A meta-analysis. *Brain Cogn* (2008) **67**:351–9. doi:10.1016/j.bandc.2008.02.005
103. Pedersen A, Rist F. Implicit memory in schizotypal subjects and normal controls: effects of a secondary task on sequence learning. *Percept Mot Skills* (2001) **92**:349–67. doi:10.2466/pms.2001.92.2.349
104. Ferraro FR, Okerlund M. Implicit memory of nonclinicla schizotypal individuals. *Percept Mot Skills* (1995) **80**:371–6. doi:10.2466/pms.1995.80.2.371
105. Bernard JA, Seidler RD, Hassevoort KM, Benson BL, Welsh RC, Wiggins JL, et al. Resting state cortico-cerebellar functional connectivity networks: a comparison of anatomical and self-organizing map approaches. *Front Neuroanat* (2012) **6**:31. doi:10.3389/fnana.2012.00031

106. Schlerf JE, Verstynen TD, Ivry RB, Spencer RMC. Evidence of a novel somatopic map in the human neocerebellum during complex actions. *J Neurophysiol* (2010) **103**:3330–6. doi:10.1152/jn.01117.2009
107. Block H, Celnik P. Stimulating the cerebellum affects visuomotor adaptation but not intermanual transfer of learning. *Cerebellum* (2013) **12**:781–93. doi:10.1007/s12311-013-0486-7
108. Schlerf JE, Galea JM, Bastian AJ, Celnik P. Dynamic modulation of cerebellar excitability for abrupt, but not gradual, visuomotor adaptation. *J Neurosci* (2012) **32**:11610–7. doi:10.1523/JNEUROSCI.1609-12.2012
109. Anguera JA, Bernard JA, Jaeggi SM, Buschkuehl M, Benson BL, Jennett S, et al. The effects of working memory resource depletion and training on sensorimotor adaptation. *Behav Brain Res* (2013) **228**:107–15. doi:10.1016/j.bbr.2011.11.040.The
110. Anguera JA, Reuter-Lorenz PA, Willingham DT, Seidler RD. Failure to engage spatial working memory contributes to age-related declines in visuomotor learning. *J Cogn Neurosci* (2011) **23**:11–25. doi:10.1162/jocn.2010.21451
111. Stoodley CJ, Valera EM, Schmahmann JD. Functional topography of the cerebellum for motor and cognitive tasks: an fMRI study. *Neuroimage* (2012) **59**:1560–70. doi:10.1016/j.neuroimage.2011.08.065
112. Leiner HC, Leiner AL, Dow RS. The human cerebro-cerebellar system: its computing, cognitive, and language skills. *Behav Brain Res* (1991) **44**:113–28. doi:10.1016/S0166-4328(05)80016-6
113. Kelly RM, Strick PL. Cerebellar loops with motor cortex and prefrontal cortex of a nonhuman primate. *J Neurosci* (2003) **23**:8432–44.
114. Akkal D, Dum RP, Strick PL. Supplementary motor area and presupplementary motor area: targets of basal ganglia and cerebellar output. *J Neurosci* (2007) **27**:10659–73. doi:10.1523/JNEUROSCI.3134-07.2007
115. Dum RP, Strick PL. An unfolded map of the cerebellar dentate nucleus and its projections to the cerebral cortex. *J Neurophysiol* (2003) **89**:634–9. doi:10.1152/jn.00626.2002
116. Strick PL, Dum RP, Fiez JA. Cerebellum and nonmotor Function. *Annu Rev Neurosci* (2009) **32**:413–34. doi:10.1146/annurev.neuro.31.060407.125606
117. Krienen FM, Buckner RL. Segregated fronto-cerebellar circuits revealed by intrinsic functional connectivity. *Cereb Cortex* (2009) **19**:2485–97. doi:10.1093/cercor/bhp135
118. Habas C, Kamdar N, Nguyen D, Prater K, Beckmann CF, Menon V, et al. Distinct cerebellar contributions to intrinsic connectivity networks. *J Neurosci* (2009) **29**:8586–94. doi:10.1523/JNEUROSCI.1868-09.2009
119. O'Reilly JX, Beckmann CF, Tomassini V, Ramnani N, Johansen-Berg H. Distinct and overlapping functional zones in the cerebellum defined by resting state functional connectivity. *Cereb Cortex* (2010) **20**:953–65. doi:10.1093/cercor/bhp157
120. Bernard JA, Peltier SJ, Benson BL, Wiggins JL, Jaeggi SM, Buschkuehl M, et al. Dissociable functional networks of the human dentate nucleus. *Cereb Cortex* (2014) **24**:2151–9. doi:10.1093/cercor/bht065
121. Buckner RL, Krienen FM, Castellanos A, Diaz JC, Yeo BTT. The organization of the human cerebellum estimated by intrinsic functional connectivity. *J Neurophysiol* (2011) **106**(5):2322–45. doi:10.1152/jn.00339.2011
122. Salmi J, Pallesen KJ, Neuvonen T, Brattico E, Korvenoja A, Salonen O, et al. Cognitive and motor loops of the human cerebro-cerebellar system. *J Cogn Neurosci* (2010) **22**:2663–76. doi:10.1162/jocn.2009.21382
123. E KH, Chen SH, Ho MH, Desmond JE. A meta-analysis of cerebellar contributions to higher cognition from PET and fMRI studies. *Hum Brain Mapp* (2012) **35**(2):593–615. doi:10.1002/hbm.22194
124. Stoodley CJ, Schmahmann JD. Evidence for topographic organization in the cerebellum of motor control versus cognitive and affective processing. *Cortex* (2010) **46**:831–44. doi:10.1016/j.cortex.2009.11.008
125. Balsters JH, Whelan CD, Robertson IH, Ramnani N. Cerebellum and cognition: evidence for the encoding of higher order rules. *Cereb Cortex* (2013) **23**:1433–43. doi:10.1093/cercor/bhs127
126. Strakowski SM, Delbello MP, Adler CM. The functional neuroanatomy of bipolar disorder: a review of neuroimaging findings. *Mol Psychiatry* (2005) **10**:105–16. doi:10.1038/sj.mp.4001585
127. DelBello MP, Strakowski SM, Zimmerman ME, Hawkins JM, Sax KW. MRI analysis of the cerebellum in bipolar disorder: a pilot study. *Neuropsychopharmacology* (1999) **21**:63–8. doi:10.1016/S0893-133X(99)00026-3
128. Mills NP, Delbello MP, Adler CM, Strakowski SM. MRI analysis of cerebellar vermal abnormalities in bipolar disorder. *Am J Psychiatry* (2005) **162**:1530–2. doi:10.1176/appi.ajp.162.8.1530
129. Escalona PR, Early B, McDonald WM, Doraiswamy M, Shah SA, Husain MM, et al. Reduction of cerebellar volume in major depression: a controlled MRI study. *Depression* (1993) **1**:156–8. doi:10.1002/depr.3050010307
130. Schmitt A, Schulenberg W, Bernstein H-G, Steiner J, Schneider-Axmann T, Yeganeh-Doost P, et al. Reduction of gyrification index in the cerebellar vermis in schizophrenia: a post-mortem study. *World J Biol Psychiatry* (2011) **12**(Suppl 1):99–103. doi:10.3109/15622975.2011.598379
131. Deicken RF, Feiwell R, Schuff N, Soher B. Evidence for altered cerebellar vermis neuronal integrity in schizophrenia. *Psychiatry Res* (2001) **107**:125–34. doi:10.1016/S0925-4927(01)00103-2
132. Maloku E, Covelo IR, Hanbauer I, Guidotti A, Kadriu B, Hu Q, et al. Lower number of cerebellar Purkinje neurons in psychosis is associated with reduced reelin expression. *Proc Natl Acad Sci U S A* (2010) **107**:4407–11. doi:10.1073/pnas.0914483107
133. Lohr JB, Jeste DV. Cerebellar pathology in schizophrenia? A neuronometric study. *Biol Psychiatry* (1986) **21**:865–75. doi:10.1016/0006-3223(86)90259-3
134. Andersen BO, Pakkenberg B. Stereological quantitation in cerebella from people with schizophrenia stereological quantitation in cerebella from people with schizophrenia. *Br J Psychiatry* (2003) **182**:354–61. doi:10.1192/bjp.02.65
135. Andersen BB, Fabricius K, Gundersen HJG, Jelsing J, Stark K. No change in neuron numbers in the dentate nucleus of patients with schizophrenia estimated with a new stereological method – the smooth fractionator. *J Anat* (2004) **205**:313–21. doi:10.1111/j.0021-8782.2004.00337.x
136. Ichimiya T, Okubo Y, Suhara T, Sudo Y. Reduced volume of the cerebellar vermis in neuroleptic-naive schizophrenia. *Biol Psychiatry* (2001) **49**:20–7. doi:10.1016/S0006-3223(00)01081-7
137. Keller A, Castellanos FX, Vaituzis C, Jeffries NO, Giedd JN, Rapoport JL. Progressive loss of cerebellar volume in childhood-onset schizophrenia. *Am J Psychiatry* (2003) **160**:128–33. doi:10.1176/appi.ajp.160.1.128
138. Bottmer C, Bachmann S, Pantel J, Essig M, Amann M, Schad LR, et al. Reduced cerebellar volume and neurological soft signs in first-episode schizophrenia. *Psychiatry Res* (2005) **140**:239–50. doi:10.1016/j.pscychresns.2005.02.011
139. James AC, James S, Smith DM, Javaloyes A. Cerebellar, prefrontal cortex, and thalamic volumes over two time points in adolescent-onset schizophrenia. *Am J Psychiatry* (2004) **161**:1023–9. doi:10.1176/appi.ajp.161.6.1023
140. Okugawa G, Sedvall GC, Agartz I. Smaller cerebellar vermis but not hemisphere volumes in patients with chronic schizophrenia. *Am J Psychiatry* (2003) **160**:1614–7. doi:10.1176/appi.ajp.160.9.1614
141. Loeber RT, Cintron CM, Yurgelun-Todd D. Morphometry of individual cerebellar lobules in schizophrenia. *Am J Psychiatry* (2001) **158**:952–4. doi:10.1176/appi.ajp.158.987.952
142. Greenstein D, Lenroot R, Clausen L, Chavez A, Vaituzis C, Tran L, et al. Cerebellar development in childhood onset schizophrenia and non-psychotic siblings. *Psychiatry Res* (2011) **193**:131–7. doi:10.1016/j.pscychresns.2011.02.010
143. Borgwardt SJ, Riecher-Rössler A, Dazzan P, Chitnis X, Aston J, Drewe M, et al. Regional gray matter volume abnormalities in the at risk mental state. *Biol Psychiatry* (2007) **61**:1148–56. doi:10.1016/j.biopsych.2006.08.009
144. Pantelis C, Velakoulis D, McGorry PD, Wood SJ, Suckling J, Phillips LJ, et al. Neuroanatomical abnormalities before and after onset of psychosis: a cross-sectional and longitudinal MRI comparison. *Lancet* (2003) **361**:281–8. doi:10.1016/S0140-6736(03)12323-9
145. Kim D-J, Kent JS, Bolbecker AR, Sporns O, Cheng H, Newman SD, et al. Disrupted modular architecture of cerebellum in schizophrenia: a graph theoretic analysis. *Schizophr Bull* (2014) **40**:1216–26. doi:10.1093/schbul/sbu059
146. Weier K, Fonov V, Lavoie K, Doyon J, Collins DL. Rapid automatic segmentation of the human cerebellum and its lobules (RASCAL)-Implementation and application of the patch-based label-fusion technique with a template library to segment the human cerebellum. *Hum Brain Mapp* (2014) **35**:5026–39. doi:10.1002/hbm.22529
147. Park MTM, Pipitone J, Baer LH, Winterburn JL, Shah Y, Chavez S, et al. Derivation of high-resolution MRI atlases of the human cerebellum at 3T and segmentation using multiple automatically generated templates. *Neuroimage* (2014) **95C**:217–31. doi:10.1016/j.neuroimage.2014.03.037

148. Diedrichsen J, Balsters JH, Flavell J, Cussans E, Ramnani N. A probabilistic MR atlas of the human cerebellum. *Neuroimage* (2009) **46**:39–46. doi:10.1016/j.neuroimage.2009.01.045
149. Diedrichsen J. A spatially unbiased atlas template of the human cerebellum. *Neuroimage* (2006) **33**:127–38. doi:10.1016/j.neuroimage.2006.05.056
150. Bernard JA, Peltier SJ, Wiggins JL, Jaeggi SM, Buschkuehl M, Fling BW, et al. Disrupted cortico-cerebellar connectivity in older adults. *Neuroimage* (2013) **83**:103–19. doi:10.1016/j.neuroimage.2013.06.042

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Received: 28 July 2014; accepted: 25 October 2014; published online: 25 November 2014.
*Citation: Bernard JA and Mittal VA (2014) Cerebellar-motor dysfunction in schizophrenia and psychosis-risk: the importance of regional cerebellar analysis approaches. Front. Psychiatry **5**:160. doi: 10.3389/fpsyt.2014.00160*
This article was submitted to Schizophrenia, a section of the journal Frontiers in Psychiatry.

frontiers in PSYCHIATRY

REVIEW ARTICLE
published: 23 December 2014
doi: 10.3389/fpsyt.2014.00185

Neurological soft signs in the clinical course of schizophrenia: results of a meta-analysis

Silke Bachmann[1,2†], Christina Degen[3*†], Franz Josef Geider[3] and Johannes Schröder[3]

[1] *Clienia Littenheid AG, Littenheid, Switzerland*
[2] *Department of Psychiatry, Psychotherapy, and Psychosomatics, University of Halle, Halle, Germany*
[3] *Section of Geriatric Psychiatry, Institute of Gerontology, University of Heidelberg, Heidelberg, Germany*

Edited by:
Sebastian Walther, University Hospital of Psychiatry, Switzerland

Reviewed by:
Raymond C. Chan, Chinese Academy of Sciences, China
Lise Docx, University of Antwerp, Belgium

****Correspondence:***
Christina Degen, University Hospital Heidelberg, Section of Geriatric Psychiatry, Voßstraße 4, Heidelberg 69115, Germany
e-mail: christina.degen@med.uni-heidelberg.de

† Silke Bachmann and Christina Degen have contributed equally to this work.

Neurological soft signs (NSS) comprise subtle deficits in sensory integration, motor coordination, and sequencing of complex motor acts, which are typically observed in the majority of schizophrenia patients, including chronic cases and neuroleptic-naïve first-episode patients. However, recent studies clearly demonstrate that NSS are not a static feature of schizophrenia but vary in the clinical course of the disorder. This effect was investigated in a meta-analysis based on 17 longitudinal studies published between 1992 and 2012. Studies included between 10 and 93 patients with schizophrenia spectrum disorders (total number 787) with follow-up periods between 2 and 208 weeks. Beside the Neurological Examination Scale, the Cambridge Neurological Inventory and the Heidelberg NSS Scale were used to assess NSS. All but three studies found NSS to decrease in parallel with remission of psychopathological symptoms. This effect was more pronounced in patients with a remitting compared to a non-remitting, chronic course (Cohen's d 0.81 vs. 0.15) and was significantly correlated with length of the follow-up period ($r = -0.64$) but not with age ($r = 0.28$). NSS scores did not decrease to the level typically observed in healthy controls. From a clinical perspective, NSS may therefore be used to identify subjects at risk to develop schizophrenia and to monitor disease progression.

Keywords: NSS, schizophrenia, chronicity, course, outcome

INTRODUCTION

Neurological soft signs (NSS) refer to subtle neurological abnormalities comprising deficits in sensory integration, motor coordination, and sequencing of complex motor acts (1–3). It is generally accepted that NSS are more prevalent in schizophrenia patients compared to healthy subjects. They have consistently been demonstrated in neuroleptic-naïve first-episode patients, i.e., prior to medication exposure, supporting the assumption that NSS constitute an intrinsic feature of schizophrenia. This notion is underlined by increased NSS scores in high-risk subjects, such as relatives of schizophrenic patients, or in the unaffected co-twins of monozygotic twin-pairs discordant for schizophrenia (4–6).

Already in 1980, Torrey found NSS to be associated with more chronic and severe forms of the illness (7). Along these lines, Manschreck and Ames (1) reported significant correlations between NSS and psychopathological symptoms in a cross-sectional study. These findings led to the hypothesis that NSS are not a static feature of schizophrenia but vary in the clinical course of the disorder, which was investigated in the late 1980s and early 1990s by the Heidelberg group (3, 8). Patients with an acute exacerbation of schizophrenia were investigated on admission, the seventh day of treatment, and following remission of acute symptoms, prior to discharge. Results clearly demonstrated a decrease of NSS scores with remission of psychopathological symptoms. Similarly, the parallel decrease of NSS and psychopathological symptoms during neuroleptic treatment was confirmed in drug-naïve first-episode (FE) patients (9) and during the long-term course up to 4 years (10–12). When contrasted with healthy controls, NSS scores obtained in schizophrenia patients remained significantly higher during follow-up indicating that NSS comprise both state- and trait-features.

These findings are pivotal to our concept of NSS and indicate that cerebral sites important for motor and sensory functions are directly involved in schizophrenia. From a clinical standpoint, NSS may be used to monitor the disease process or to identify subjects with an increased liability toward schizophrenia. However, these conclusions are based on the above observation of the remission of NSS with psychopathological symptoms during the clinical course. In the present study, we therefore analyzed the development of NSS in the course of schizophrenia as it was described in longitudinal studies. We hypothesized NSS scores to decrease with remission of psychopathological symptoms and expected this effect to be more pronounced in patients with a more favorable compared to a chronic, non-remitting course of disorder.

METHODS

Studies on the longitudinal course of NSS in schizophrenia were identified by conventional bibliographic search in particular of the reference list of previous papers (13) and by a *pubmed* search performed in August 2014 using the keywords: "schizophrenia," "NSS," "course," "follow-up," "chronicity." These procedures yielded 16 relevant publications, which reported the data necessary to calculate effect sizes (Cohen's d). An additional data set was contributed on request (14). Studies were published between 1992 and 2012; they differed with respect to the clinical settings and the rating instruments used (**Table 1**). Eleven studies assessed NSS with the

Table 1 | Overview of studies.

Study	Follow-up (weeks)	Scale	N	Diagnostic groups	Mean age (SD)	Medication	NSS t1	NSS t2	Effect size	Psy. path t1	Psy. path t2	Effect size 2
Bachmann et al. (10)	56	HD, PANSS	39	FE (DSM-IV)	27 (7.7)	Clin. Needs	15.7 (7.1)	10.1 (7.9)	0.75	52.4 (25.6)	52 (12.4)	0.02
			22	HC	28 (3.8)		4.8 (3.3)	4.6 (3.9)	0.06	*	*	
			18	NR (DSM-IV)	*		13.8 (7.2)	13.5 (8.7)	0.04	52.6 (14.9)	63.9 (32.6)	−0.48
			21	R (DSM-IV)	*		17.3 (6.8)	7.2 (5.8)	1.60	51.4 (10)	42.6 (10.8)	0.85
Boks et al. (18)	104	NES, PANSS	29	FE (DSM-IV)	26.9 (6.3)		7.5 (7.1)	8.9 (5.5)	−0.22	*	*	*
Buchanan et al. (19)	10	NES, BPRS	16	CH (DSM-III)	34.1 (6.8)	Clozapine	16.2 (5.9)	16.8 (8.2)	−0.09	11.4 (5.8)	9.4 (5.2)	0.34
	10		15	CH (DSM-III)	34.6 (9.1)	Haloperidol	14.5 (6.3)	15.1 (7.5)	−0.09	12.6 (5.3)	12.0 (5.1)	0.12
Chen et al. (20)	156	motor CNI	93	FE (DSM-IV)	31.2 (9.6)	Haloperidol imitially	1.87 (2)	1.45 (2.2)	0.2	*	*	*
			68	HC	32 (8.4)		*	*		*	*	*
Cuesta et al. (21)	26	NES	77	FE (DSM-IV)	30.1 (10)	Risperidone or olanzapine	17.1 (9.4)	9.9 (6.8)	0.89	10.1 (3.5)[a]	1.6 (2.1)	3.04
		SAPS, SANS			30.6 (6.2)		*	*		8 (5.9)[b]	4.7 (4.9)	0.61
Emsley et al. (14)	52	NES	15	FE (DSM-IV)	28.1 (8.5)		6.2 (3.57)	5.1 (4.0)	0.3	*	*	*
Mangot and Sawant (22)	52	NES	40	FE (ICD-10)	35.5 (11.9)		8.5 (7.1)	3.3 (4.1)	0.93	*	*	*
Mayoral et al. (16)	104	NES	29	FE (DSM-IV)	15.7 (1.6)		23.2 (9.1)	19.2 (9.9)	0.42	*	*	*
			22	HC	15.2 (1.6)		12.2 (6.7)	9.7 (5.2)	0.42	*	*	*
Mayoral et al. (17)	104	NES, PANSS	69	FE (DSM-IV)	15.5 (1.8)		25.2 (9.6)	19.9 (8.1)	0.6	66.2 (17.9)	58 (23.3)	0.40
			80	HC	15.2 (1.9)		11.1 (7.2)	9.2 (5.5)	0.3	*	*	*
Mittal et al. (23)	6	Quitkin, BPRS	19	SCHIZ (DSM-III-R)	36.3 (5.4)	Haloperidol	6.3 (0.9)	5.3 (0.8)	1.18	34.3 (2.1)	22.4 (2.2)	5.53
Prikryl et al. (11)	52	NES, PANSS	92	FE (ICD-10)	25.3 (5.5)		*	*		*	*	
			20	NR	*		6.5 (4.1)	4.2 (4.1)	0.56	88.4 (19.9)	84.7 (21.6)	0.18
			72	R	*		5.3 (5.9)	2.7 (3.4)	0.56	97.6 (22.5)	43.8 (11.1)	3.20
Prikryl et al. (12)	208	NES	68	FE (ICD-10)	22.5 (5)		6.3 (5.1)	6.8 (6.6)	−0.09	97 (23.2)	51.5 (19)	2.16
			29	NR	*		6.6 (4.8)	10.1 (7.6)	−0.56	*	*	*
			39	R	*		6 (5.4)	4.4 (4.5)	0.32	*	*	*
Schröder et al. (3)	variable	HD, BPRS	27	CH (DSM-III)	36 (12.1)	Clin. needs	27.8 (9.2)	22.1 (7.1)	0.7	*	*	*
			23	R	28.9 (8.9)		23.5 (8.3)	13 (4.7)	1.61	*	*	*
Schröder et al. (8)	variable	HD, BPRS	32	CH and R (DSM-III)	32 (9)	Clin. needs	21.3 (8.3)	11.5 (5.7)	1.4	46.1 (7.3)	32.1 (5.7)	2.15
Schröder et al. (9)	4	HD, BPRS	15	FE (DSM-III-R)	29.2 (9.4)	Benperidol	16.2 (7.5)	10 (4.7)	1.02	48.1 (6.6)	35.7 (7.7)	1.75
			8	R			15.5 (7.2)	9.3 (4.6)	1.05	49.4 (7.8)	32.5 (7.2)	2.25
			7	NR			17.0 (8.5)	10.9 (5.0)	0.9	46.7 (5.2)	39.3 (7.4)	1.18
Sevincok and Topaloglu (24)	2	NES, PANSS	10	CH (DSM-IV)	24.5 (*)	Olanzapine	19.1 (13.2)	14.7 (12.5)	0.34	78.8 (19.9)	58.0 (13.1)	1.26
Whitty et al. (25)	26	NES, PANSS	79	FE (DSM-IV)	23.4 (*)		15.6 (9.7)	12.5 (7.3)	0.36	83.3 (20.1)	58.4 (15.1)	1.41

*HD, Heidelberg NSS Scale; PANSS, Positive and Negative Syndrome Scale; NES, Neurological Evaluation Scale; BPRS, Brief Psychiatric Rating Scale; CNI, Cambridge Neurological Inventory; SAPS, Scale for the assessment of positive symptoms; SANS, Scale for the assessment of negative symptoms; FE, first-episode psychosis; HC, healthy controls; NR, non-remitters; R, remitters; CH, chronic schizophrenics; SCHIZ, schizophrenia patients; [a], SAPS, [b], SANS, *, missing values.*

Neurological Examination Scale (NES) and four with the Heidelberg scale (HD). One study used the Cambridge Neurological Inventory [CNI (15)]. Two studies examined adolescents (16, 17). The latter results will be discussed separately, since the motor system has not entirely maturated at this age. Separate effect sizes were calculated for NSS and psychopathology before estimating mean effect sizes for patients with remitting and chronic courses.

RESULTS

Included studies are summarized in **Table 1**. The number of patients per study ranged between 10 and 93 (total number 787); 12 studies solely included FE patients, 2 studies focused on adolescents. Patients' clinical course was characterized as either remitting or non-remitting/chronic in eight studies; in one study only the diagnosis "schizophrenia" was conveyed. Follow-up periods ranged between 2 weeks and 4 years. In nine studies, the examination commenced during the acute psychotic episodes; in four of those a reexamining after remission of acute symptoms, prior to discharge, took place. Standardized neuroleptic treatment was prescribed in five studies, namely high potency butyrophenones (haloperidol or benperidol), risperidone, or olanzapine.

All but three studies described a decrease of NSS in the clinical course. Eleven studies included an assessment of the clinical course. Patients with remitting symptoms showed a steeper decrease of NSS scores (mean effect size: Cohen's d 0.81) than patients with an unfavorable or chronic course (mean effect size: Cohen's d 0.15), who even exhibited an increase in scores. Overall, effect sizes (Cohen's d) ranged between −0.56 (patients with an unfavorable course) and 1.61 (patients with a remitting course treated for an acute episode) with an overall mean effect size of Cohen's d 0.53. Ratings of psychopathological symptoms paralleled the development of NSS scores but were only reported in 11 of the 17 studies. Moreover, data on the distinction between negative and positive symptom scores were provided by five studies only (12, 17, 21, 23, 24). In FE patients, as a group, a moderate effect size was present (Cohen's d 0.42). Similar effect sizes (Cohen's d: 0.42–0.60) were reported in adolescent patients with FE psychosis. Effect sizes were significantly ($p < 0.05$) correlated with length of the follow-up period ($r = -0.64$, $p = 0.001$) but not with age ($r = 0.28$).

DISCUSSION

The present meta-analysis revealed two main findings: (i) a confirmation that NSS scores decrease in the clinical course of schizophrenia with remission of psychopathological symptoms; and (ii) an indication that this effect is more pronounced in patients with a remitting course than in those with non-remitting schizophrenia.

Despite numerous methodological differences, all but three studies found decreasing NSS scores during the clinical course with remission of acute schizophrenia symptoms. Boks et al. (18) reported NSS to increase in a group of 29 FE patients, who were investigated 2 years apart (Cohen's d −0.22). They assigned this effect to a subgroup of patients with a more severe form of the disorder or a regression to the mean and stressed the importance of the relatively small sample size when interpreting their findings. A marginal increase of NSS scores (Cohen's d −0.09) in patients with chronic schizophrenia was also reported by Buchanan and colleagues (19) in 31 patients who received haloperidol or clozapine for 10 weeks. Jahn et al. (26) identified increasing NSS scores only in a small subgroup of patients in whom symptoms deteriorated. Their study could not be included in our meta-analysis, because only median values had been documented. Prikryl et al. (12) systematically followed FE patients for 4 years and found NSS to marginally increase (Cohen's d −0.09) when the whole group of 68 patients was considered. This effect, however, was caused by a subgroup of patients developing chronic schizophrenia (Cohen's d −0.56) while NSS in those with a remitting course decreased (Cohen's d 0.32). A similar build-up of NSS scores has been described by Chen et al. (27) in 43 patients with chronic schizophrenia over the course of 3 years. Their study was not included here, because total NSS scores had not been provided. Taken together, effect sizes for the decrease of NSS scores ranged from Cohen's d 0.04 to Cohen's d 1.61 with an average of Cohen's d 0.64. The smallest effects were seen in patients with non-remitting schizophrenia (mean effect size for non-remitting patients: Cohen's d 0.15) while more pronounced effect sizes were observed in patients with a remitting course (mean effect size for remitting patients: Cohen's d 0.81). However, only eight studies assessed the clinical course while nine just characterized patients as FE or solely documented DSM diagnoses.

A most interesting question arises from the finding that the decrease of NSS and the decrease of symptoms parallel each other. Unfortunately, this relationship could not be analyzed any further by meta-analytic tools. Both NSS and psychopathology had been assessed with several different instruments, and symptom scores were not provided in several publications.

The effect sizes reported in FE studies appeared to be lower than those found in patients with a remitting and even those with a chronic course. However, only four of the available FE studies drew a distinction between remitting and non-remitting patients. In addition, the exact timing of the first examination after study intake has to be taken into account. While Prikryl and colleagues (11, 12) and Schröder et al. (9) examined NSS at or shortly after admission, i.e., in an acute psychotic state – Bachmann et al. (10) conducted the first NSS examination after clinical stabilization, before discharge. This may well have had an impact on the findings since NSS scores typically show a significant decrease with remission of the acute symptoms (3, 8). The important meta-analysis of cross-sectional NSS studies by Chan et al. (28) found effect sizes of patients vs. controls comparisons to be moderated by duration of illness. One may hypothesize that NSS continue to improve or worsen during the course following the first manifestation of the disease; a hypothesis, which conforms to the above cited studies, namely the differences, which emerged between patients with a remitting vs. a non-remitting, chronic course.

The decrease of NSS with clinical stabilization during the course was more pronounced in patients with a favorable than with a non-remitting course (3, 9, 10, 11, and 12); therefore, NSS scores could be identified as course predictors. However, even after remission of the acute illness, NSS scores remained significantly higher than in healthy controls. These findings demonstrate that NSS in schizophrenia are both trait- and state-related. NSS persistence and deterioration in patients with a chronic course of the disorder clearly point to a progression of corresponding cerebral changes

as demonstrated in a recent study from the Heidelberg group (29). From a clinical perspective, NSS may therefore be used to identify subjects at risk to develop chronic schizophrenia. It is well known, that total NSS scores in schizophrenia are mainly due to motor and sensory subscores. Unfortunately, only 7 of 17 studies (10–12, 16, 17, 21, 25) reported subscores; therefore, a more detailed meta-analysis could not be performed.

A decrease of NSS scores with clinical stabilization was also reported in adolescent patients with FE psychosis (16, 17), i.e., during an age in which the motor and sensory systems are still not entirely maturated. Both studies of the Mayoral group also found a decrease of NSS in the control group over the 2-year-study period and a higher score level in patients on comparison. Authors attributed their findings to an overall developmental delay caused by rather than a direct consequence of the disease.

Potentially confounding variables include different NSS rating scales and study designs. Although different, the various NSS scales are comparable with regard to the majority of subscales and sensitivity (27); moreover, the potential impact of the respective psychometric differences is at least partially addressed by the longitudinal designs of the studies. Neuroleptic treatment was standardized in 6 of the included 17 studies only. However, the vast majority of studies discussed here report decreasing NSS in patients treated with any neuroleptic compound. Furthermore, it is known that NSS are not caused by neuroleptic medication (30, 31). In our study, a negative correlation between effect sizes and length of follow-up period was identified. It is plausible that clinical stabilization occurs in the beginning of the follow-up interval leaving mostly non-remitting patients. As a result, effect sizes of NSS decrease with length of inspected interval.

Along with this, Buchanan et al. (19) did not find meaningful or even significant differences in chronic patients receiving either clozapine or haloperidol while Schröder et al. (9) demonstrated a decrease of NSS in FE patients who received a conventional neuroleptic. As discussed above, the timing of the first examination may even have great importance, in particular as the exact starting points were not defined in a number of studies. The decrease of NSS was correlated with age, although this did not reach statistical significance. The meta-analysis of cross-sectional studies (28) did not find NSS difference scores between patients and healthy controls to be moderated by age when only studies with the NES were entered into the meta-analysis. Although both findings correspond with respect to the direction of change, the impact of age and other potential moderators as sex and education, or cognitive reserve (Urbanowitsch et al., submitted) on NSS needs to be further analyzed. Against the background of a relatively small number of studies included here, the respective methodological questions call for a large multicenter longitudinal study in FE patients. Such an endeavor would not only be suitable to dissect the decrease of NSS in the clinical course confirmed in this meta-analysis but could also serve to define the state and trait characteristics of NSS more precisely. The potential impact of motor development could be addressed in adolescent patients; moreover, neuroimaging studies could be designed to better understand the role of motor and sensory cortical sites in schizophrenia.

From a clinical standpoint, the decrease of NSS with clinical stabilization may be used to monitor disease progression or to identify subjects with an increased liability toward schizophrenia in general and more chronic, unfavorable courses in particular. As a phenomenon, NSS point at the involvement of motor and sensory cerebral sites in the disorder. Since NSS correspond to impaired motor and sensory functions like motor coordination, they can be used to further develop and optimize physical training programs, which are already part of the routine therapeutic repertoire.

ACKNOWLEDGMENTS

This study was supported by the Dietmar-Hopp Foundation, Walldorf, Germany. We are grateful to Robin Emsley/Stellenbosch, South Africa for providing his valuable data.

REFERENCES

1. Manschreck TC, Ames D. Neurologic features and psychopathology in schizophrenic disorders. *Biol Psychiatry* (1984) **19**:703–19.
2. Heinrichs DW, Buchanan RW. Significance and meaning of neurological signs in schizophrenia. *Am J Psychiatry* (1988) **145**:11–8.
3. Schröder J, Niethammer R, Geider F-J, Reitz C, Binkert M, Jauss M, et al. Neurological soft signs in schizophrenia. *Schizophr Res* (1992) **6**:25–30. doi:10.1016/0920-9964(91)90017-L
4. Niethammer R, Weisbrod M, Schiesser S, Grothe J, Maier S, Peter U, et al. Genetic Influence on laterality in schizophrenia? A twin study of neurological soft signs. *Am J Psychiatry* (2000) **157**:272–4. doi:10.1176/appi.ajp.157.2.272
5. Torrey EF, Taylor EH, Bracha HS, Bowler AE, McNeil TF, Rawlings RR, et al. Prenatal origin of schizophrenia in a subgroup of discordant monozygotic twins. *Schizophr Bull* (1994) **20**:423–32. doi:10.1093/schbul/20.3.423
6. Rossi A, De Cataldo S, Di Michele V, Manna V, Ceccoli S, Stratta P, et al. Neurological soft signs in schizophrenia. *Br J Psychiatry* (1990) **157**:735–9. doi:10.1192/bjp.157.5.735
7. Torrey EF. Neurological abnormalities in schizophrenic patients. *Biol Psychiatry* (1980) **15**:381–9.
8. Schröder J, Tittel A, Stockert A, Karr M. Memory deficits in subsyndromes of chronic schizophrenia. *Schizophr Res* (1996) **21**:19–26. doi:10.1016/0920-9964(96)00027-8
9. Schröder J, Silvestri S, Bubeck B, Karr M, Demisch S, Scherrer S, et al. D2 Dopamine receptor up-regulation, treatment response, neurological soft signs, and extrapyramidal side effects in schizophrenia: a follow-up study with ^{123}I-iodobenzamide single photon emission computed tomography in the drug-naïve state and after neuroleptic treatment. *Biol Psychiatry* (1998) **43**:660–5.
10. Bachmann S, Bottmer C, Schröder S. Neurological soft signs in first-episode schizophrenia: a follow-up study. *Am J Psychiatry* (2005) **162**:2337–43. doi:10.1176/appi.ajp.162.12.2337
11. Prikryl R, Ceskova E, Kasparek T, Kucerova H. Neurological soft signs and their relationship to 1-year outcome in first-episode schizophrenia. *Eur Psychiatry* (2007) **22**:449–504. doi:10.1016/j.eurpsy.2007.03.012
12. Prikryl R, Ceskova E, Tronerova S, Kasparek T, Prikrylova Kucerova H, Ustohal L, et al. Dynamics of neurological soft signs and its relationship to clinical course in patients with first-episode schizophrenia. *Psychiatry Res* (2012) **200**:67–72. doi:10.1016/j.psychres.2012.03.008
13. Bachmann S, Schröder J. Neurological soft signs in schizophrenia: a review on the state- versus trait-perspective.
14. Emsley R, Turner HJ, Oosthuizen PP, Carr J. Neurological abnormalities in first-episode schizophrenia: temporal stability and clinical and outcome correlates. *Schizophr Res* (2005) **75**:35–44. doi:10.1016/j.schres.2004.06.014
15. Chen EYH, Shapleske J, Luque R, McKenna PJ, Hodges JR, Calloway SP, et al. The Cambridge Neurological Inventory: a clinical instrument for assessment of soft neurological signs in psychiatric patients. *Psychiatry Res* (1995) **56**:183–204. doi:10.1016/0165-1781(95)02535-2
16. Mayoral M, Bombin I, Zabala A, Robes O, Moreno D, Parellada M, et al. Neurological soft signs in adolescents with first-episode psychosis: two-year followup. *Psychiatry Res* (2008) **161**:344–8. doi:10.1016/j.psychres.2007.07.013
17. Mayoral M, Bombin I, Castro-Fornieles J, Gonzales-Pinto A, Otero S, Parellada M, et al. Longitudinal study of neurological soft signs in first-episode early-onset psychosis. *J Child Psychol Psychiatry* (2012) **53**:323–31. doi:10.1111/j.1469-7610.2011.02475.x

18. Boks MPM, Selten JP, Leask S, Van den Bosch RJ. The 2-year stability of neurological soft signs after a first episode of non-affective psychosis. *Eur Psychiatry* (2006) **21**:288–90. doi:10.1016/j.eurpsy.2005.09.004
19. Buchanan RW, Koeppl P, Breier A. Stability of neurological signs with clozapine treatment. *Biol Psychiatry* (1994) **36**:198–200. doi:10.1016/0006-3223(94)91225-4
20. Chen EYH, Hui CLM, Chan RCK, Dunn ELW, Miao MYK, Yeung WS, et al. A 3-year prospective study of neurological soft signs in first episode schizophrenia. *Schizophr Res* (2005) **75**:45–54. doi:10.1016/j.schres.2004.09.002
21. Cuesta MJ, Jalon EG, Campos MS, Peralta V. Cognitive effectiveness of olanzapine and risperidone in first episode psychosis. *Br J Psychiatry* (2009) **194**:439–45. doi:10.1192/bjp.bp.108.055137
22. Mangot AG, Sawant NS. First episode schizophrenia: neurological abnormalities and prognosis. *German J Psychiatry*. Reprinted from the German Journal of Psychiatry. Available from: http://www.gjpsy.uni-goettingen.de
23. Mittal VA, Hasenkamp W, Sanfilipo M, Wieland S, Angrist B, Rotrosen J, et al. Relation of neurological soft signs to psychiatric symptoms in schizophrenia. *Schizophr Res* (2007) **94**:37–44. doi:10.1016/j.schres.2007.04.017
24. Sevincok L, Topaloglu B. Neurological soft signs and positive treatment response to olanzapine in chronic schizophrenia. *Prog Neuropsychoph* (2006) **30**:141–3. doi:10.1016/j.pnpbp.2005.06.012
25. Whitty P, Clarke M, Browne S, McTique O, Kamali M, Feeney L, et al. Prospective evaluation of neurological soft signs in first-episode schizophrenia in relation to psychopathology: state versus trait phenomena. *Psychol Med* (2003) **33**:1479–84. doi:10.1017/S0033291703008225
26. Jahn T, Hubmann W, Karr M, Mohr F, Schlenker R, Heidenreich T, et al. Motoric neurological soft signs and psychopathological symptoms in schizophrenic psychoses. *Psychiatr Res* (2006) **142**:191–9. doi:10.1016/j.psychres.2002.12.003
27. Chen EYH, Kwok CL, Au JWY, Chen RYL, Lau BST. Progressive deterioration of soft neurological signs in chronic schizophrenic patients. *Acta Psychiatr Scand* (2000) **102**:342–9. doi:10.1034/j.1600-0447.2000.102005342.x
28. Chan RCK, Xu T, Heinrichs RW, Yu Y, Wang Y. Neurological soft signs in schizophrenia: a meta-analysis. *Schizophr Bull* (2009) **36**:1089–104. doi:10.1093/schbul/sbp011
29. Kong L, Bachmann S, Thomann PA, Essig M, Schröder J. Neurological soft signs and gray matter changes: a longitudinal analysis in first-episode schizophrenia. *Schizophr Res* (2012) **134**:27–32. doi:10.1016/j.schres.2011.09.015
30. Browne S, Clarke M, Gervin M, Lane A, Waddington JL, Larkin C, et al. Determinants of neurological dysfunction in first episode schizophrenia. *Psychol Med* (2000) **30**:1433–41. doi:10.1017/S003329179900286X
31. Keshavan MS, Sanders RD, Sweeney JA, Diwadkar VA, Goldstein G, Pettegrew JW, et al. Diagnostic specificity and neuroanatomical validity of neurological abnormalities in first-episode psychosis. *Am J Psychiatry* (2003) **160**:1298–304. doi:10.1176/appi.ajp.160.7.1298

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Received: 31 October 2014; paper pending published: 15 November 2014; accepted: 08 December 2014; published online: 23 December 2014.
*Citation: Bachmann S, Degen C, Geider FJ and Schröder J (2014) Neurological soft signs in the clinical course of schizophrenia: results of a meta-analysis. Front. Psychiatry **5**:185. doi: 10.3389/fpsyt.2014.00185*
This article was submitted to Schizophrenia, a section of the journal Frontiers in Psychiatry.

frontiers in PSYCHIATRY

OPINION ARTICLE
published: 09 January 2015
doi: 10.3389/fpsyt.2014.00190

Movement disorders and psychosis, a complex marriage

Peter N. van Harten[1,2]*, P. Roberto Bakker[1,2], Charlotte L. Mentzel[1,2], Marina A. Tijssen[3] and Diederik E. Tenback[1,3]

[1] Psychiatric Centre GGz Centraal, Innova, Amersfoort, Netherlands
[2] School for Mental Health and Neuroscience, Maastricht University, Maastricht, Netherlands
[3] Department of Neurology, University Medical Center Groningen, University of Groningen, Groningen, Netherlands
*Correspondence: pnvanharten@gmail.com

Edited by:
Manuel Morrens, University of Antwerp, Belgium

Reviewed by:
Bernhard J. Mitterauer, Volitronics-Institute for Basic Research Psychopathology and Brain Philosophy, Austria
Manuel Morrens, University of Antwerp, Belgium

Keywords: movement disorders, psychotic disorders, tardive dyskinesia, schizophrenia, instrumental assessment

Most clinicians relate parkinsonism and dyskinesia directly to acute and tardive drug-induced movement disorders. However, parkinsonism and dyskinesia are also present in antipsychotic-naïve patients with psychotic disorders. In this paper, we want to highlight the clinical value of these spontaneous movement disorders and want to discuss the concept of "non-mental signs."

ACUTE DRUG-INDUCED MOVEMENT DISORDERS

Acute drug-induced movement disorders, such as acute dystonia, parkinsonism, and akathisia, are very common side effects of dopamine blocking agents. A causal relationship between these movement disorders and antipsychotics is beyond any doubt if (i) antipsychotic-naïve psychotic patients without movement disorders receive antipsychotics and develop these side effects, (ii) they disappear after dose reduction or cessation of the antipsychotics, and (iii) this on–off mechanism can be repeated.

TARDIVE SYNDROMES

The relationship between tardive syndromes and antipsychotics is far more complex because they start after months to years of treatment with antipsychotics and can also be suppressed by antipsychotics. Tardive suggests drug induced, and also spontaneous hyperkinetic dyskinesias, such as "grimacing" and "irregular movements of tongue and lips" (and also parkinsonism), are prevalent in antipsychotic-naïve psychotic patients and have been described by Kraepelin and Bleuler more than a 100 years ago (1).

In patients with long-term use of antipsychotics, there is no test to differentiate between drug-induced tardive and spontaneous movement disorders. The prevalence of drug-induced tardive dyskinesia is substantial and increases with age, the same counts for spontaneous movement disorders such as dyskinesia, bradykinesia, and soft neurological signs related to schizophrenia (2–15). Also, a meta-analysis showed that in antipsychotic-naïve patients with schizophrenia the risk of dyskinesia and parkinsonism are three and five times higher than in healthy controls, respectively (16). Furthermore, another study in antipsychotic-naïve patients showed a prevalence of dyskinesia and parkinsonism of 13 and 18%, respectively, with the use of clinical rating scales, which increased to 20 and 28%, respectively, with the use of instrumental assessment (17).

On the other hand, several findings suggest a direct relationship between antipsychotics and tardive dyskinesia. First, non-psychiatric patients may also develop tardive dyskinesia after long-term use of dopamine blocking agents, e.g., long-term use of metoclopramide to treat nausea, or antipsychotics for insomnia (18, 19). Furthermore, in older patients receiving first-generation antipsychotics for the first time the yearly incidence of tardive dyskinesia is extremely high, over 20%, which is much higher than the incidence of spontaneous dyskinetic movement in older patients (12, 13). Also, tardive dyskinesia may disappear after cessation of antipsychotics or after a switch to clozapine. These findings suggest a direct relationship between antipsychotics and tardive dyskinesia.

Based on the studies mentioned above, it is clear that the assumption that antipsychotics are responsible for tardive dyskinesia is at least incomplete. Indeed, movement disorders can be considered an intrinsic feature of the disease process and implicate dysfunction in cortical–basal ganglia-cortical circuitry (11). The role of the antipsychotics may be modification of the disease-based motor disorder and antipsychotics can both improve and unmask primary motor abnormalities (10).

The clinical importance of spontaneous movement disorders is also emphasized by the relationship between spontaneous parkinsonism and cognitive dysfunction. In a prospective study in antipsychotic-naïve patients with first-episode psychosis, spontaneous parkinsonism at baseline showed high 6-month predictive values for cognitive impairment (9).

PATHOPHYSIOLOGY

The pathogenesis of tardive dyskinesia remains unresolved. Several hypotheses have been proposed such as dopamine 2 (D2)-receptor hypersensitivity, striatal neurodegeneration, maladaptive synaptic plasticity, and enhanced serotonin 2 (5-HT2)-receptor signaling and recently up regulation of striatal D3 receptors had been suggested in a primate model (20). Although none of these models have been confirmed sufficiently they have in common the disturbance of the balance in the motor circuit of the basal ganglia in which dopamine plays a central role. The dopamine (and possibly also the acetylcholine) dysregulation in the basal ganglia-thalamo-cortical loops may result in hyper or hypokinetic movements

whereas dopamine dysregulation in other brain areas may result in the development of psychosis (21).

Another model is based on synaptic dysregulations in which the core hypothesis is that non-functional astrocytic receptors may cause an unconstrained synaptic information flux, such that glia lose their modulatory function in glial–neuronal interaction (tripartite synapses) (22). Dysregulation of tripartite synapses would occur with dopamine synapses throughout the brain and may be related to both motoric and mental symptoms.

CLINICAL RELEVANCE

The clinical relevance for measuring dyskinesia and/or parkinsonism in first-episode psychotic disorders is based on several follow-up studies showing that they predict poor prognosis, increased cognitive impairment, poorer response to antipsychotics, and an increased risk for drug-induced movement disorders (9, 11, 23).

Also, in individuals at ultra-high risk for psychosis (UHR group) the assessment of spontaneous movement disorders may be highly relevant. Several studies suggest that subtle abnormal movements are predictive for conversion to psychosis later. The current screening strategy focuses on mental symptoms and has a limited conversion rate to psychosis, around 20–40%, giving to many false positives. It could be that adding measurement of movement disorders to the screening strategy will reduce the number of false positives. Indeed, studies show (i) more abnormal movements in the UHR group than in the control group, (ii) a relationship between the severity of the abnormal movements and the severity of prodromal signs (positive, negative, and total) at baseline, (iii) a relationship between an increase in severity of the abnormal movements with an increase of prodromal signs during follow-up, and (iv) a higher risk to convert to psychosis at follow-up in the UHR groups with abnormal movements at baseline than those without (24, 25).

Detection of those in the UHR group who will convert to psychosis is relevant as a meta-analysis showed the effectiveness of some interventions to prevent or postpone a first-episode of psychosis (26).

RELATIONSHIP BETWEEN MOVEMENT, COGNITIVE, AND EMOTIONAL DISORDERS

Obeso et al. describe that the basal ganglia are intimately connected with the cortex through several segregated but parallel loops. These loops are subdivided into motor, associative (cognitive), and limbic (emotional) domains and are related to the control of movement, behavior and cognition, and reward and emotions, respectively. When one or more of these circuits become dysfunctional they can generate movement disorders, behavioral, cognitive abnormalities, or mood changes. They suggest, for example that the combination of nigrostriatal denervation and dopaminergic drugs, as seen in Parkinson's disease, may induce behavioral disorders such as impulse control disorders and that this may be the behavioral counterpart of hyperkinetic disorders such as dyskinesia (27). Similar with this idea is the concept that dysregulation of dopaminergic activity in dopaminergic related brain areas lead to positive and negative symptoms in psychotic disorders and that these symptoms are the behavioral counterpart of dyskinesia and bradykinesia, respectively. It has been suggested that psychotic patients with abnormal movements, compared to those without, have a more severely dysregulated dopamine system (28). This may explain the clustering of abnormal movements with cognitive and negative symptoms and the relationship with poor prognosis. Also, a correlation has been found between tardive dyskinesia and cognitive symptoms (29). It could be that drug-induced movement disorders are related to a more vulnerable dopamine system and subsequently to an increased risk for dyskinesia and negative and cognitive symptoms. In line with the vulnerability concept is the relationship found between early extrapyramidal symptoms such as parkinsonism and an increased risk for developing tardive dyskinesia in the future (30, 31). However, the underlying dysfunction(s) that provoke(s) spontaneous movement abnormalities, tardive dyskinesia, cognitive impairment, negative symptoms, and emotional disturbances remains unclear. It is unlikely that one neurotransmitter, i.e., dopamine is responsible. Although, dysfunction of the modulatory activity of dopamine plays an important role in the clinical manifestations mentioned above, also acetylcholine, which is released across the entire striatal network by striatal cholinergic interneurons, has neuromodulatory properties in the basal ganglia. Furthermore, other neurotransmitters are involved, such as glutamatergic inputs from the cerebral cortex and thalamus to striatal spiny projection neurons (21).

NON-MENTAL SIGNS

Based on the presence of motor, associative (cognitive), and limbic (emotional) loops in the basal ganglia, we want to introduce the concept of non-mental signs (dyskinesia and parkinsonism) in psychotic disorders. This concept is the equivalent of non-motor signs (mood disorders, apathy, anxiety, etc.) in Parkinson's disease (32). The severity of non-mental signs may have a direct relationship with the severity of dysregulation of the dopamine system. An advantage of non-mental signs is the possibility to measure them objectively and several research groups have developed instruments to measure these non-mental signs instrumentally. Instrumental assessment of movement disorders is sensitive, valid, and reliable and a motor test battery that will quantify the main motor functions has been suggested (33–38). In addition, instrumental measurement can also detect subclinical movement abnormalities and these assessments may be used to predict the course of a (pre)psychotic disorder and can be used to develop preventive strategies.

In conclusion, we suggest classifying movement disorders in psychotic disorders or in UHR groups as non-mental signs. Instrumental measurements of these non-mental signs are objective and have clinical implications for prognosis, diagnosis, and treatment of psychotic disorders. In UHR groups adding non-mental signs to the screening strategy may reduce the number of false positives. Non-mental signs could become one of the first biomarkers in psychiatric screening programs.

REFERENCES

1. Bleuler E. *Lehrbuch der Psychiatrie*. Berlin: Springer (1916).
2. Tarbox SI, Pogue-Geile MF. Spontaneous dyskinesia and familial liability to schizophrenia. *Schizophr Res* (2006) **81**:125–37. doi:10.1016/j.schres.2005.09.013
3. McCreadie RG, Padmavati R, Thara R, Srinivasan TN. Spontaneous dyskinesia and parkinsonism

in never-medicated, chronically ill patients with schizophrenia: 18-month follow-up. *Br J Psychiatry* (2002) **181**:135–7. doi:10.1192/bjp.181.2.135
4. Fenton WS. Prevalence of spontaneous dyskinesia in schizophrenia. *J Clin Psychiatry* (2000) **61**(Suppl 4):10–4. doi:10.1002/mds.23050
5. Koning JP, Tenback DE, van Os J, Aleman A, Kahn RS, van Harten PN. Dyskinesia and parkinsonism in antipsychotic-naive patients with schizophrenia, first-degree relatives and healthy controls: a meta-analysis. *Schizophr Bull* (2010) **36**:723–31. doi:10.1093/schbul/sbn146
6. Bervoets C, Docx L, Sabbe B, Vermeylen S, Van Den Bossche MJ, Morsel A, et al. The nature of the relationship of psychomotor slowing with negative symptomatology in schizophrenia. *Cogn Neuropsychiatry* (2014) **19**:36–46. doi:10.1080/13546805.2013.779578
7. Morrens M, Hulstijn W, Sabbe B. Psychomotor slowing in schizophrenia. *Schizophr Bull* (2007) **33**:1038–53. doi:10.1093/schbul/sbl051
8. Walther S, Strik W. Motor symptoms and schizophrenia. *Neuropsychobiology* (2012) **66**:77–92. doi:10.1159/000339456
9. Cuesta MJ, Sanchez-Torres AM, de Jalon EG, Campos MS, Ibanez B, Moreno-Izco L, et al. Spontaneous parkinsonism is associated with cognitive impairment in antipsychotic-naive patients with first-episode psychosis: a 6-month follow-up study. *Schizophr Bull* (2014) **40**:1164–73. doi:10.1093/schbul/sbt125
10. Peralta V, de Jalon EG, Campos MS, Cuesta MJ. Phenomenological differences between spontaneous and drug-related extrapyramidal syndromes in patients with schizophrenia-spectrum disorders. *J Clin Psychopharmacol* (2013) **33**:438–40. doi:10.1097/JCP.0b013e31828f62b0
11. Whitty PF, Owoeye O, Waddington JL. Neurological signs and involuntary movements in schizophrenia: intrinsic to and informative on systems pathobiology. *Schizophr Bull* (2009) **35**:415–24. doi:10.1093/schbul/sbn126
12. Jeste DV, Caligiuri MP, Paulsen JS, Heaton RK, Lacro JP, Harris MJ, et al. Risk of tardive dyskinesia in older patients. A prospective longitudinal study of 266 outpatients. *Arch Gen Psychiatry* (1995) **52**:756–65. doi:10.1001/archpsyc.1995.03950210050010
13. Dolder CR, Jeste DV. Incidence of tardive dyskinesia with typical versus atypical antipsychotics in very high risk patients. *Biol Psychiatry* (2003) **53**:1142–5. doi:10.1016/S0006-3223(03)00170-7
14. van Harten PN, Matroos GE, Hoek HW, Kahn RS. The prevalence of tardive dystonia, tardive dyskinesia, parkinsonism and akathisia: the Curacao extrapyramidal syndromes study: I. *Schizophr Res* (1996) **19**:195–203. doi:10.1016/0920-9964(95)00096-8
15. van Harten PN, Hoek HW, Matroos GE, van Os J. Incidence of tardive dyskinesia and tardive dystonia in African Caribbean patients on long-term antipsychotic treatment: the Curacao extrapyramidal syndromes study V. *J Clin Psychiatry* (2006) **67**:1920–7. doi:10.4088/JCP.v67n1212
16. Koning JP, Kahn RS, Tenback DE, van Schelven LJ, van Harten PN. Movement disorders in nonpsychotic siblings of patients with nonaffective psychosis. *Psychiatry Res* (2011) **188**:133–7. doi:10.1016/j.psychres.2011.01.005
17. Cortese L, Caligiuri MP, Malla AK, Manchanda R, Takhar J, Haricharan R. Relationship of neuromotor disturbances to psychosis symptoms in first-episode neuroleptic-naive schizophrenia patients. *Schizophr Res* (2005) **75**:65–75. doi:10.1016/j.schres.2004.08.003
18. Rao AS, Camilleri M. Review article: metoclopramide and tardive dyskinesia. *Aliment Pharmacol Ther* (2010) **31**:11–9. doi:10.1111/j.1365-2036.2009.04189.x
19. Anderson SL, Vande Griend JP. Quetiapine for insomnia: a review of the literature. *Am J Health Syst Pharm* (2014) **71**:394–402. doi:10.2146/ajhp130221
20. Mahmoudi S, Levesque D, Blanchet PJ. Upregulation of dopamine D3, not D2, receptors correlates with tardive dyskinesia in a primate model. *Mov Disord* (2014) **29**:1125–33. doi:10.1002/mds.25909
21. Bergman H, Kimura M, Wickens JR. Modulation of striatal circuits by dopamine and acetylcholine. In: Grillner S, Graybiel AM, editors. *Microcircuits: The Interface Between Neurons and Global Brain Function.* Cambridge: The MIT Press (2006). p. 149–63.
22. Mitterauer B. Pathophysiology of schizophrenia based on impaired glial-neuronal interactions. *Open J Med Psychol* (2014) **3**:126–40. doi:10.4236/ojmp.2014.32016
23. Silvestri S, Seeman MV, Negrete JC, Houle S, Shammi CM, Remington GJ, et al. Increased dopamine D2 receptor binding after long-term treatment with antipsychotics in humans: a clinical PET study. *Psychopharmacology (Berl)* (2000) **152**:174–80. doi:10.1007/s002130000532
24. Mittal VA, Walker EF. Movement abnormalities predict conversion to axis I psychosis among prodromal adolescents. *J Abnorm Psychol* (2007) **116**:796–803. doi:10.1037/0021-843X.116.4.796
25. Mittal VA, Tessner KD, Trottman HD, Esterberg M, Dhrub SH, Simeonova DI, et al. Movement abnormalities and the progression of prodromal symptomatology in adolescents at risk for psychotic disorders. *J Abnorm Psychol* (2007) **116**:260–7. doi:10.1037/0021-843X.116.2.260
26. van der Gaag M, Smit F, Bechdolf A, French P, Linszen DH, Yung AR, et al. Preventing a first episode of psychosis: meta-analysis of randomized controlled prevention trials of 12 month and longer-term follow-ups. *Schizophr Res* (2013) **149**:56–62. doi:10.1016/j.schres.2013.07.004
27. Obeso JA, Rodriguez-Oroz MC, Stamelou M, Bhatia KP, Burn DJ. The expanding universe of disorders of the basal ganglia. *Lancet* (2014) **384**:523–31. doi:10.1016/S0140-6736(13)62418-6
28. Tenback DE. *An Epidemiological Approach to Elucidate Doapminergic Mechanism in Tardive Dyskinesia in Schizophrenia.* Maastricht: Maastricht University (2006).
29. Waddington JL, Youssef HA. Cognitive dysfunction in chronic schizophrenia followed prospectively over 10 years and its longitudinal relationship to the emergence of tardive dyskinesia. *Psychol Med* (1996) **26**:681–8. doi:10.1017/S0033291700037697
30. Tenback DE, van Harten PN, Slooff CJ, van Os J. Evidence that early extrapyramidal symptoms predict later tardive dyskinesia: a prospective analysis of 10,000 patients in the European Schizophrenia Outpatient Health Outcomes (SOHO) study. *Am J Psychiatry* (2006) **163**:1438–40. doi:10.1176/appi.ajp.163.8.1438
31. Bakker PR, van Harten PN, van Os J. Antipsychotic-induced tardive dyskinesia and polymorphic variations in COMT, DRD2, CYP1A2 and MnSOD genes: a meta-analysis of pharmacogenetic interactions. *Mol Psychiatry* (2008) **13**(5):544–56. doi:10.1038/sj.mp.4002142
32. Rizos A, Martinez-Martin P, Odin P, Antonini A, Kessel B, Kozul TK, et al. Characterizing motor and non-motor aspects of early-morning off periods in Parkinson's disease: an international multicenter study. *Parkinsonism Relat Disord* (2014) **20**(11):1231–5. doi:10.1016/j.parkreldis.2014.09.013
33. Koning JP, Tenback DE, Kahn RS, Van Schelven LJ, Van Harten PN. Instrument measurement of lingual force variability reflects tardive tongue dyskinesia. *J Med Eng Technol* (2010) **34**:71–7. doi:10.3109/03091900903402105
34. Dean DJ, Teulings HL, Caligiuri M, Mittal VA. Handwriting analysis indicates spontaneous dyskinesias in neuroleptic naive adolescents at high risk for psychosis. *J Vis Exp* (2013) **81**:e50852. doi:10.3791/50852
35. Caligiuri MP, Teulings HL, Dean CE, Niculescu AB, Lohr J. Handwriting movement analyses for monitoring drug-induced motor side effects in schizophrenia patients treated with risperidone. *Hum Mov Sci* (2009) **28**:633–42. doi:10.1016/j.humov.2009.07.007
36. Dean CE, Russell JM, Kuskowski MA, Caligiuri MP, Nugent SM. Clinical rating scales and instruments: how do they compare in assessing abnormal, involuntary movements? *J Clin Psychopharmacol* (2004) **24**:298–304. doi:10.1097/01.jcp.0000125681.97466.e7
37. Docx L, Sabbe B, Provinciael P, Merckx N, Morrens M. Quantitative psychomotor dysfunction in schizophrenia: a loss of drive, impaired movement execution or both? *Neuropsychobiology* (2013) **68**:221–7. doi:10.1159/000355293
38. Morrens M, Docx L, Walther S. Beyond boundaries: in search of an integrative view on motor symptoms in schizophrenia. *Front Psychiatry* (2014) **5**:145. doi:10.3389/fpsyt.2014.00145

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Received: 11 October 2014; paper pending published: 12 October 2014; accepted: 12 December 2014; published online: 09 January 2015.
*Citation: van Harten PN, Bakker PR, Mentzel CL, Tijssen MA and Tenback DE (2015) Movement disorders and psychosis, a complex marriage. Front. Psychiatry **5**:190. doi: 10.3389/fpsyt.2014.00190*
This article was submitted to Schizophrenia, a section of the journal Frontiers in Psychiatry.

frontiers in PSYCHIATRY

OPINION ARTICLE
published: 14 October 2014
doi: 10.3389/fpsyt.2014.00145

Beyond boundaries: in search of an integrative view on motor symptoms in schizophrenia

Manuel Morrens[1,2]*, Lise Docx[1,2] and Sebastian Walther[3]

[1] Collaborative Antwerp Psychiatric Research Institute, University of Antwerp, Antwerp, Belgium
[2] Psychiatric Center Alexian Brothers, Boechout, Belgium
[3] University Hospital of Psychiatry, University of Bern, Bern, Switzerland
*Correspondence: manuel.morrens@uantwerpen.be

Edited by:
Mihaly Hajos, Yale University School of Medicine, USA

Reviewed by:
Gretchen Hermes, Yale University, USA
Mihaly Hajos, Yale University School of Medicine, USA

Keywords: motor, psychomotor disorders, schizophrenia, catatonia, neurological soft signs, extrapyramidal signs, assessment methods

MOTOR SYMPTOMS OF SCHIZOPHRENIA

Schizophrenia is typically conceived as an illness characterized by positive, negative, and cognitive symptoms. However, most schizophrenia patients also display a wide range of symptoms characterized by aberrant motor functioning. Symptoms of schizophrenia that fit this description are catatonic features, the motoric neurological soft signs (NSS), extrapyramidal symptoms (EPS), psychomotor slowing, and reduced motor activity.

CATATONIA

Catatonic symptoms form a heterogeneous group of motor, emotional, and behavioral symptoms. Mostly in line with historical reports, several recent studies demonstrate a prevalence of the catatonic features in 5–32% of schizophrenia patients (1, 2). Although the incidence of catatonia in schizophrenia may have decreased somewhat, the syndrome is still highly prevalent but often underdiagnosed (2).

NEUROLOGICAL SOFT SIGNS

Neurological soft signs are a heterogeneous cluster of subtle neurological signs that are generally divided into four subcategories: sensory integration, primitive reflexes, motor coordination, and sequencing of complex motor acts, the latter two being considered "motoric" NSS (3). NSS have been demonstrated in up to 97 and 100% of neuroleptic naive and medicated first-episode patients, respectively (1).

PSYCHOMOTOR SLOWING

Psychomotor slowing refers to the slowing of various motor processes such as gross (e.g., gait) and fine motor (e.g., writing) movement, speech, and facial expression. Our group conducted a series of studies in which impairments in different aspects of psychomotor functioning were slowed, including planning, initiation, and execution of movements (4, 5).

Several studies assessed the amount of motor activity by means of actigraphy, which consistently demonstrated reduced motor activity levels in schizophrenia patients (2, 6). This reduction in spontaneous motor behavior was associated with negative symptom severity (7, 8).

EXTRAPYRAMIDAL SYMPTOMS

Akathisia, Parkinsonism, dyskinesia, and dystonia are considered EPS. Although these clinical features are most persistently linked to antipsychotic pharmacotherapy, there is growing consensus that the use of antipsychotic medication is not the main cause but a contributing factor to motor abnormalities in schizophrenia (9). In a systematic review (10), a median rate of 9% of spontaneous dyskinesia and a median rate of 17% of spontaneous Parkinsonism was reported in antipsychotic-naive first-episode patients, thus positioning EPS as highly prevalent intrinsic symptoms of schizophrenia. Spontaneous Parkinsonism and abnormal involuntary movements are also found at increased frequencies in unaffected first degree relatives of schizophrenia patients (11).

POSITIONING MOTOR SYMPTOMS IN SCHIZOPHRENIA

When considering all motor symptoms, recent research demonstrates that 40–80% of the schizophrenic patients present with at least one categorically defined motor syndrome (12, 13). Moreover, these symptoms are associated to the patients' social, clinical, and functional outcome (14) and can be differentiated from positive, negative, and cognitive symptoms (15). As a result, it can be argued that motor deficits deserve recognition as a fourth symptom cluster of schizophrenia.

However, despite the increasing focus on these motor symptom cluster, the positioning of the motor syndrome is hampered by some important limitations.

First, predefined motor syndromes such as catatonia, NSS, or EPS typically stem from different research traditions, and are typically investigated separately. Hence, establishing the interrelations of the different components of motor functioning as well as their associations to other symptom groups such as negative and cognitive syndromes is limited by the fact that studies investigating more than one motor symptom cluster are scarce.

Second, the different psychomotor symptom clusters are assessed with different techniques. NSS are typically assessed by use of a neurological evaluation, psychomotor slowing is consistently gauged by use of instrumental tasks such as a finger tapping test or computerized writing tasks, and catatonia and EPS are commonly appraised using clinical rating scales. As has been demonstrated, interrelations between motor symptoms are confounded by the applied assessment technique (13).

An important artifact of the existence of parallel research lines and of

the boundaries imposed by the predefined symptom clusters and their assessment instruments is the conceptual overlap between the motor syndromes. For example, rigidity is a symptom assessed by EPS, catatonia, and NSS rating scales. Similarly, psychomotor slowing, clinically recognized as bradykinesia, can also be seen as a parkinsonian sign, or as a mild form of stupor (16). This overlap not only exists between the different motor syndromes, but also with cognitive and negative symptomatology. Decreased spontaneous movement is one of the features of the negative syndrome in schizophrenia. Similarly, several neuropsychological tasks that are sensitive for higher order cognitive deficits (e.g., symbol digit substitution test or trail making tasks) are often used to assess psychomotor slowing (15).

Some may argue these predefined motor symptom clusters have internal validity, since several of the symptoms of these clusters (e.g., catatonic symptoms) co-occur and these symptom clusters tend to respond to different treatment strategies: acute catatonia responds to benzodiazepines or electroconvulsive treatment; EPS rather responds to anticholinergics, although it should be noted akathisia also responds to benzodiazepines. Nevertheless, the delineation between the clusters can be questioned. Much confusion exists on which motor symptoms constitute catatonia, leading to different tools that include from only 7 up to 40 signs or symptoms. Moreover, Krüger and colleagues (17) demonstrated that catatonic presentation may vary depending on the underlying pathology, thus challenging catatonia as a homogeneous construct. Besides, as mentioned before, a strong overlap seems to exist between these motor syndromes, justifying a reappraisal of motor functioning in schizophrenia based on the deconstruction of the barriers between predefined motor symptom clusters.

Very few studies focused on the neurobiological underpinnings of motor deficits in schizophrenia, although abnormalities in both cortical (anterior cingulate cortex, supplementary motor area, premotor cortex) and subcortical (basal ganglia, thalamus) regions as well as brain stem and cerebellum have been implicated [for review, see Ref. (2)].

Table 1 | Proposed classification of motor symptomatology in schizophrenia.

Function domain	Quantitative deficits	Qualitative deficits
Positioning	Posturing, rigidity	Catalepsy, tremor, tandem walk deficits
Mobility	Reduced gait, diminished movements, stupor	Manneristic walk
Manipulation	Fine motor slowing, reduced facial expression	Stereotypy, mannerisms, fine motor sequence deficits, echopraxia
Oral motor functions	Reduced speech	Orofacial dyskinesia, echolalia
Visual functions	Gaze impersistence, staring	Blepharospasms

MOTOR AND PSYCHOMOTOR FUNCTIONS

A much more fruitful and systematic approach may be to evaluate patients based on the different domains of motor and psychomotor functions. Rainforth and colleagues (18) classified motor functioning in five main motor skill domains: positioning, mobility, manipulation, oral motor functions, and oculomotor control. Positioning refers to the ability to assume and maintain a position as well as to maintain postural control. Mobility encompasses every action that aims at traveling from one point to another (walking, climbing, crawling). Manipulation implies every interaction with your own body (e.g., clapping hands, scratching face, . . .) or interaction with objects (e.g., playing tennis, drawing, writing a phrase, . . .). Oral motor functions include speech and other oral functions such as drinking or eating. Finally, visual functions mainly encompass blinking and the ability to fix and orient a gaze.

Some of these domains (e.g., positioning) are rather basic motor skills and do not necessarily need higher order cognitive control and may mostly be executed unconsciously while other motor domains (e.g., manipulation of objects) are heavily impacted by cognitive processes involved in the planning, initiation, execution, and monitoring of these motor acts. Consequently, the functions involved in these latter motor acts are sometimes referred to as psychomotor functions. Several studies have aimed at further delineating the subprocesses involved in psychomotor functioning (4, 13, 19).

These basic motor and psychomotor functions can be affected both on a quantitative and a qualitative level; functions can be increased/reduced (quantitative) but there may also be a breach with normal motor function leading to symptoms characterized by behavior not seen in healthy patients (qualitative). A parallel comparison can be made with cognitive functioning; patients display quantitative cognitive deficits (e.g., reduced memory or attention functioning), but also qualitative cognitive abnormalities can emerge (e.g., perseveration, neologisms and, arguably, delusional thinking).

This frame of reference allows for repositioning all motor symptoms, independent of whether they are traditionally recognized as catatonic symptoms, EPS, NSS, psychomotor slowing, or diminished motor activity (see **Table 1**). Note that this table does not aim to exhaustively list all motor symptoms.

ASSESSING MOTOR SKILLS AND PSYCHOMOTOR FUNCTIONS

An atheoretical evaluation of motor functioning in schizophrenia making use of a more broad assessment methodology (or combination of assessment techniques) that address all these motor function domains may result in a more complete appraisal of motor and psychomotor deficits in schizophrenia, both on the quantitative and qualitative level. Such an approach has the advantage of giving a general overview of all deficits and may confirm or nuance the existing classification of motor symptomatology. Their relationship with and delineation from negative and cognitive symptoms can be evaluated more properly.

Rating scales have been developed [e.g., the Rogers Scale (20)] that score symptoms

from more than one motor syndrome, although these scales still tend to focus on qualitative abnormalities and to a much lesser degree on quantitative abnormalities. As a result, they do not give a complete overview of motor functioning. On the other hand, test batteries evaluating general motor functioning can be considered, e.g., the Bruininks-Oseretsky Test of motor proficiency (BOT-2) or the movement assessment battery for children (Movement ABC-2). Typically, these batteries aim to provide a comprehensive view on ones motor functioning an even generate a motor quotient, a motor equivalent of the intelligence quotient (IQ). Included tests typically assess fine and gross motor functions such as (static and dynamic) balance and precision, walking speed, force, bilateral coordination, or visuomotor control (21). Since motor skills traditionally have been viewed in relation to the normal motor development of a young child (18), these batteries have been used to assess motor deficiencies in children, typically in children with developmental disorder, or intellectual disability, but have almost no use in adults. The Bruininks motor ability test (BMAT), an adult adaptation of the BOT-2, has recently been developed, but to our knowledge has never been investigated in adult psychiatric patient samples. Nevertheless, such an instrument with a focus on broad motor functioning is more sensitive to quantitative deficits, but in its turn lacks the capacity to assess more specific qualitative deficits.

Therefore, in order to have a more complete assessment of motor deficits in schizophrenia patients (as well as patients with other psychiatric illnesses), a test battery that encompasses on one hand tests assessing the different motor functions quantitatively and on the other assessments addressing qualitative deficits is needed. A consensus on which qualitative deficits should be included and on which assessment techniques to use in such a battery will contribute to a uniformed and more complete assessment of motor functioning in psychiatric illnesses. A large study in different psychiatric populations would consequently be needed to further validate this new motor test battery.

Chen and colleagues (22) developed a comprehensive neurological evaluation scale, the Cambridge Neurological Inventory, which addresses many of the motor functions on both a quantitative and qualitative level. This interesting tool assesses different domains of motor functioning, and constitutes of three subscales: (1) Speech, eye movements, and extremity examinations, (2) Soft signs examinations, and (3) assessments of posture and movements, including catatonia and tardive dyskinesia. Sadly, after its introduction, this instrument has mostly been used for its soft signs subscale (23, 24) whereas the total scale seems to have sunk into oblivion. This scale may prove to be a good starting point to further development of the proposed wide-ranging motor test battery. In addition, the battery should make use of instrumental assessment techniques.

Given that (psycho)motor deficits have been observed in neuroleptic-naïve first-episode patients, in stabilized young patients and in chronic patients, the use of this battery would be relevant in all phases of the illness (1, 9, 13). Such a battery may be used to further investigate the neurobiological underpinnings of these deficits, as well as to differentiate intrinsic motor deficits from the antipsychotic-induced motor side effects.

CONCLUSION

A wide range of motor abnormalities can be observed in schizophrenia patients and their high prevalence warrant recognition of this motor symptom cluster. However, predefined motor syndromes such as catatonia are hampered by many limitations, and a more holistic approach may be needed to further our understanding of the motor syndrome. Research focused on assessing a wide range of motor functions encompassing both basic motor skills and higher order psychomotor functions is needed. The development of a motor test battery that will both quantify the main motor functions and assess qualitative deficits may contribute to new insights in motor functioning of psychiatric patients including those suffering from schizophrenia.

REFERENCES

1. Morrens M, Hulstijn W, Sabbe BG. Psychomotor symptoms in schizophrenia: the importance of a forgotten syndrome. *Tijdschr Psychiatr* (2008) **50**:713–24.
2. Walther S, Strik W. Motor symptoms and schizophrenia. *Neuropsychobiology* (2012) **66**:77–92. doi: 10.1159/000339456
3. Jahn T, Hubmann W, Karr M, Mohr F, Schlenker R, Heidenreich T, et al. Motoric neurological soft signs and psychopathological symptoms in schizophrenic psychoses. *Psychiatry Res* (2006) **142**:191–9. doi:10.1016/j.psychres.2002.12.003
4. Morrens M, Hulstijn W, Matton C, Madani Y, Van Bouwel L, Peuskens J, et al. Delineating psychomotor slowing from reduced processing speed in schizophrenia. *Cogn Neuropsychiatry* (2008) **13**:457–71. doi:10.1080/13546800802439312
5. Morrens M, Hulstijn W, Sabbe B. The effects of atypical and conventional antipsychotics on reduced processing speed and psychomotor slowing in schizophrenia: a cross-sectional exploratory study. *Clin Ther* (2008) **30**:684–92. doi:10.1016/j.clinthera.2008.04.012
6. Walther S, Federspiel A, Horn H, Razavi N, Wiest R, Dierks T, et al. Alterations of white matter integrity related to motor activity in schizophrenia. *Neurobiol Dis* (2011) **42**:276–83. doi:10.1016/j.nbd.2011.01.017
7. Walther S, Koschorke P, Horn H, Strik W. Objectively measured motor activity in schizophrenia challenges the validity of expert ratings. *Psychiatry Res* (2009) **169**:187–90. doi:10.1016/j.psychres.2008.06.020
8. Walther S, Ramseyer F, Horn H, Strik W, Tschacher W. Less structured movement patterns predict severity of positive syndrome, excitement, and disorganization. *Schizophr Bull* (2014) **40**:585–91. doi:10.1093/schbul/sbt038
9. Peralta V, Cuesta MJ. Neuromotor abnormalities in neuroleptic-naive psychotic patients: antecedents, clinical correlates, and prediction of treatment response. *Compr Psychiatry* (2011) **52**:139–45. doi:10.1016/j.comppsych.2010.05.009
10. Pappa S, Dazzan P. Spontaneous movement disorders in antipsychotic-naive patients with first-episode psychoses: a systematic review. *Psychol Med* (2009) **39**:1065–76. doi:10.1017/S0033291708004716
11. Koning JP, Kahn RS, Tenback DE, Van Schelven LJ, Van Harten PN. Movement disorders in nonpsychotic siblings of patients with nonaffective psychosis. *Psychiatry Res* (2011) **188**:133–7. doi:10.1016/j.psychres.2011.01.005
12. Peralta V, Campos MS, De Jalon EG, Cuesta MJ. Motor behavior abnormalities in drug-naive patients with schizophrenia spectrum disorders. *Mov Disord* (2010) **25**:1068–76. doi:10.1002/mds.23050
13. Docx L, Morrens M, Bervoets C, Hulstijn W, Fransen E, De Hert M, et al. Parsing the components of the psychomotor syndrome in schizophrenia. *Acta Psychiatr Scand* (2012) **126**:256–65. doi:10.1111/j.1600-0447.2012.01846.x
14. Peralta V, Moreno-Izco L, Sanchez-Torres A, Garcia De Jalon E, Campos MS, Cuesta MJ. Characterization of the deficit syndrome in drug-naive schizophrenia patients: the role of spontaneous movement disorders and neurological soft signs. *Schizophr Bull* (2014) **40**:214–24. doi:10.1093/schbul/sbs152

15. Morrens M, Hulstijn W, Sabbe B. Psychomotor slowing in schizophrenia. *Schizophr Bull* (2007) **33**:1038–53. doi:10.1093/schbul/sbl051
16. Morrens M, Hulstijn W, Lewi P, Sabbe B. Bleuler revisited: psychomotor slowing in schizophrenia as part of a catatonic symptom cluster. *Psychiatry Res* (2008) **161**:121–5. doi:10.1016/j.psychres.2008.01.017
17. Kruger S, Bagby RM, Hoffler J, Braunig P. Factor analysis of the catatonia rating scale and catatonic symptom distribution across four diagnostic groups. *Compr Psychiatry* (2003) **44**:472–82. doi:10.1016/S0010-440X(03)00108-1
18. Rainforth B, Giangreco M, Ruth D. Chapter 12: motor skills. In: Ford A, Schnorr R, Meyer L, Davern L, Black J, Dempsey P, editors. *The Syracuse Community-Referenced Curriculum Guide for Students with Moderate and Severe Disabilities*. Baltimore: Brookes Publishing (1989). p. 211–30.
19. Houthoofd S, Morrens M, Hulstijn W, Sabbe B. Differentiation between deviant trajectory planning, action planning, and reduced psychomotor speed in schizophrenia. *Cogn Neuropsychiatry* (2013) **18**:284–303. doi:10.1080/13546805.2012.708654
20. Lund CE, Mortimer AM, Rogers D, Mckenna PJ. Motor, volitional and behavioural disorders in schizophrenia. 1: assessment using the Modified Rogers Scale. *Br J Psychiatry* (1991) **158**(323–327):323–6. doi:10.1192/bjp.158.3.323
21. Simons J. *Introductie tot de Psychomotoriek*. Antwerpen: Garant (2006).
22. Chen EY, Shapleske J, Luque R, Mckenna PJ, Hodges JR, Calloway SP, et al. The Cambridge neurological inventory: a clinical instrument for assessment of soft neurological signs in psychiatric patients. *Psychiatry Res* (1995) **56**:183–204. doi:10.1016/0165-1781(95)02535-2
23. Cai L, Zhu X, Yi J, Bai M, Wang M, Wang Y, et al. Neurological soft signs and their relationship with measures of executive function in Chinese adolescents. *J Dev Behav Pediatr* (2013) **34**:197–203. doi:10.1097/DBP.0b013e3182825c41
24. Zhao Q, Ma YT, Lui SS, Liu WH, Xu T, Yu X, et al. Neurological soft signs discriminate schizophrenia from major depression but not bipolar disorder. *Prog Neuropsychopharmacol Biol Psychiatry* (2013) **43**:72–8. doi:10.1016/j.pnpbp.2012.12.006

Conflict of Interest Statement: Over the last 5 years, Manuel Morrens received funding for research from Johnson & Johnson Belgium, Lundbeck Belgium and Bristol Myers Squibb Belgium and contributed to scientific activities sponsored by Astra-Zeneca Belgium, Bristol Myers Squibb Belgium, Eli Lilly Belgium, Lundbeck Belgium and Johnson & Johnson Belgium. The other coauthors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Received: 29 August 2014; accepted: 26 September 2014; published online: 14 October 2014.
*Citation: Morrens M, Docx L and Walther S (2014) Beyond boundaries: in search of an integrative view on motor symptoms in schizophrenia. Front. Psychiatry **5**:145. doi: 10.3389/fpsyt.2014.00145*
This article was submitted to Schizophrenia, a section of the journal Frontiers in Psychiatry.

frontiers in PSYCHIATRY

ORIGINAL RESEARCH ARTICLE
published: 11 February 2015
doi: 10.3389/fpsyt.2015.00012

Neurological soft signs in aging, mild cognitive impairment, and Alzheimer's disease – the impact of cognitive decline and cognitive reserve

Nadja Urbanowitsch[1]*, Christina Degen[1], Pablo Toro[3] and Johannes Schröder[1,2]

[1] *Section of Geriatric Psychiatry, University of Heidelberg, Heidelberg, Germany*
[2] *Institute of Gerontology, University of Heidelberg, Heidelberg, Germany*
[3] *Department of Psychiatry, Centro Interdisciplinario de Neurociencias, School of Medicine, Pontificia Universidad Católica de Chile, Santiago, Chile*

Edited by:
Sebastian Walther, University Hospital of Psychiatry, Switzerland

Reviewed by:
Katharina Stegmayer, University Hospital of Psychiatry, Switzerland
Lise Docx, University of Antwerp, Belgium

****Correspondence:***
Nadja Urbanowitsch, Section of Geriatric Psychiatry, University of Heidelberg, Voßstraße 4, 69115 Heidelberg, Germany
e-mail: nadja.urbanowitsch@med.uni-heidelberg.de

Objectives: Neurological soft signs (NSS), i.e., minor motor and sensory changes, are a common feature in severe psychiatric disorders. We sought to establish the frequency of NSS in patients with mild cognitive impairment (MCI) and Alzheimer's disease (AD) on basis of a large population-based sample and to identify their neuropsychological correlates including cognitive reserve.

Methods: Neurological soft signs were examined using an abbreviated version of the Heidelberg NSS Scale in 221 "old" participants born between 1930 and 1932 (63 with MCI, 15 with AD, 143 healthy old controls) and 256 healthy "young" participants (born between 1950 and 1952) of the population-based interdisciplinary longitudinal study of aging. Subjects received thorough neuropsychological testing; years of school education were used as a proxy for cognitive reserve.

Results: Neurological soft signs scores were significantly ($p < 0.001$) higher in the AD patients (5.6 ± 3.11) than in the healthy old controls (2.8 ± 1.90) and in the MCI patients (3.0 ± 1.96). This result was confirmed after years of school education, which were inversely correlated ($r = -0.25$; $p < 0.001$) with NSS were entered as a covariate. In the patients, but not in the controls, NSS were significantly correlated with deficits in executive functioning and visuospatial functioning. Comparison of NSS scores between "old" (2.84 ± 1.9) and "young" (2.46 ± 1.97) controls yielded only minor, non-significant differences after education (13.86 ± 3.0 vs. 14.61 ± 2.48 years, respectively) was controlled for.

Conclusion: Our results demonstrate that NSS are frequently found in mild AD, but not in MCI. NSS refer to frontal-executive deficits and visuospatial dysfunction rather than age *per se* and can be partly compensated for by cognitive reserve.

Keywords: NSS, MCI, AD, cognitive reserve, ILSE

INTRODUCTION

Recent studies (1, 2) demonstrate that neurological soft signs (NSS) – i.e., minor motor and sensory deficits – are frequently found in Alzheimer's disease (AD) and mild cognitive impairment (MCI) as they were consistently described in other major psychiatric conditions such as bipolar disorder or especially schizophrenia (3, 4). Corresponding to the significant association found between NSS and negative symptoms in schizophrenia (5) and Seidl et al. (2) reported a significant correlation between NSS and apathy in a large group of nursing home residents ($n = 120$) with mild to severe AD. Similar to earlier reports in schizophrenia [reviewed in Ref. (6)], Seidl et al. (2) did not find NSS to be associated with neuroleptic treatment. However, other important aspects of NSS known from studies in schizophrenia – in particular, the associations of NSS with neuropsychological deficits (7–10) – were not yet tested in AD. This question is of particular importance as positive effects of physical activity on cognitive performance are generally accepted (11).

It is generally accepted that high levels of physical activity are associated with a reduced risk for developing AD potentially by facilitating the brain and cognitive reserve. Another study of our group (11) investigated muscular strength as measured by a vigorimeter and motor coordination, which was operationalized by means of the one-foot-standing test, with respect to the risk of developing MCI or AD in the interdisciplinary longitudinal study of aging (ILSE). In the framework of this prospective population-based study, subjects (born 1930–1932) were examined at three examination waves (t_1:1993/1994; t_2: 1997/1998; t_3: 2005/2007). The study demonstrated that motor coordination evaluated at t_1 but not muscular strength was a significant predictor of cognitive impairment at t_3.

Another important question refers to the nature of NSS as signs of generalized rather than discrete cerebral changes. Along with this, neuroimaging studies in schizophrenia identified a number of dispersed cerebral sites associated with NSS (12–15). Hence, one may expect to find increased NSS scores in manifest AD where

cerebral changes involve large parts of the brain rather than in MCI where cerebral changes still remain localized in the medial temporal lobe. Accordingly, NSS scores should be rather stable in the process of healthy aging since the latter does not involve major cerebral changes.

We therefore thought to investigate NSS with respect to neuropsychological deficits and school education, as a proxy of cognitive reserve and to compare NSS scores between patients with MCI or AD and healthy old controls. In addition, NSS scores obtained in the latter were compared with scores measured in young controls to identify age-related changes.

MATERIALS AND METHODS

PARTICIPANTS

The ILSE-study is based on two birth cohorts born during 1930–1932 and 1950–1952 who were randomly recruited according to community registers in the urban regions of Leipzig (Saxony) and Heidelberg/Mannheim (Palatine). The study was approved by the ethical committee of the University of Heidelberg and written informed consent after complete description of the study to the subjects was obtained. The first examinations took place between December 1993 and January 1996. Data of the present study correspond to the third examination wave, which were performed between 2005 and 2008, i.e., more than 12 years after the initiation of the study. At this time, 381 participants of the 1930–1932 cohort and 408 participants of the 1950–1952 – corresponding to more than 75 and 80%, respectively, of the original cohorts – could be reinvestigated. Participants with a current episode of major depression, substance abuse, anxiety disorder, bipolar disorder, schizophrenia, or meeting ICD 10 criteria for a cognitive disorder due to a general medical condition were excluded from the analysis since these conditions usually course with both neurological signs and cognitive deficits and may overlap with dementia. Hence, a sample of 477 participants was available for analyses comprising 256 participants of the 1950–1952 cohort and 221 participants of the 1930–1932 cohort.

Sixty-three participants out of 221 (28.51%) were diagnosed with MCI and 15 with AD (6.79%) in the 1930–1932 cohort. Because we were interested in investigating the effects of age on NSS performance 256 otherwise healthy participants from the young cohort were also included. Hence, three groups were constituted: healthy young controls, ($n = 256$), healthy old controls ($n = 143$) old-aged with MCI (MCI; $n = 63$), and old-aged with AD (AD; $n = 15$). All participants selected for the present study had complete core data sets (socio-demographic variables, diagnoses, NSS), while the thorough neuropsychological test battery could be completed in the whole group. The mini-mental state examination [MMSE, (16)] was not applied in the young cohort.

SURVEY MEASURES

All participants were carefully screened for physical and mental health by extensive clinical interviews, physical examinations, laboratory tests, and a thorough assessment of neuropsychological functioning. Cognitive assessment included the MMSE and subtests of the Nürnberger-Alters-Inventar [NAI, (17)] and the Leistungsprüfsystem (18), both of which are well-established and commonly used test batteries in Germany [for more details, see Ref. (19)]. Subjective cognitive complaints were assessed by interviewing and applying the respective items of the Nürnberger Selbsteinschätzungsliste [NSL; (20)].

Neurological soft signs were examined by using the modified version (2) of the Heidelberg Neurological Soft Signs Scale (4), which included five items, named – (a) finger-to-nose movement, (b) diadochokinesia, (c) pronation and supination, (d) finger-thumb opposition, and (e) mirror movements. The scores of the items were scaled from 0 (no prevalence) to 3 (marked prevalence), with a total score of maximum 18. The subtests were selected from the original scale based upon clinical and research experience collected with demented patients. Examination subtest had to be easy to understand by AD patients.

PSYCHIATRIC DIAGNOSES

Clinical axis I diagnoses were obtained by using the German version of the Structured Clinical Interview for the DSM-III-R [SKID I, (21)]. MCI was defined by using the aging-associated cognitive decline (AACD) criteria, which were already applied in the first two examination waves (19, 22). Diagnostic criteria for AACD have been proposed by the international psychogeriatric association (23) and include (1) subjective impairment: a report by the individual (or a reliable informant) that cognitive function has declined and (2) objective impairment in any of the following cognitive domains, as indicated by a neuropsychological test performance of at least 1 SD below normal age and educational levels: memory and learning, attention and concentration, abstract thinking (problem solving, abstraction), language, and visuospatial functioning. AD was diagnosed according to the NINCDS–ADRA (24). All diagnoses were confirmed by both specialists in old age psychiatry involved.

STATISTICAL ANALYSES

Clinical variables, NSS, and neuropsychological performances were compared between groups by calculating separate analyses of covariance (ANCOVA) with group (healthy young controls vs. healthy old controls vs. MCI vs. AD) as predictor variable and years of education as covariate. *Post hoc* comparison analyses were based on Duncan's test. The potential relations between NSS, clinical variables, and neuropsychological findings were addressed by calculating Pearson product-moment correlation coefficients, which were controlled for years of education. All computations were performed by using the 9.2 version of the SAS Software.

RESULTS

The clinical characteristics, neuropsychological performance, and total NSS scores obtained in the diagnostic groups are summarized in **Table 1**. Diagnostic groups differed significantly with respect to age and years of school education but showed no significant differences in sex distribution. As expected, AD patients scored significantly lower than MCI patients, followed by healthy old controls, on the MMSE. With respect to neuropsychological test performance, three patterns of group differences arose: performance on verbal memory, digit symbol, D2, and visuospatial thinking tests conformed to the expected order with the highest scores achieved by healthy young controls, followed by healthy old controls and MCI, and the lowest scores obtained by AD.

Table 1 | Demographic and neuropsychological characteristics by subgroup with the results of a Duncan test at the 5%-level.

	Healthy young controls ($n = 256$)	Healthy old controls ($n = 143$)	MCI ($n = 63$)	AD ($n = 15$)	F (df)	p	Duncan/Chi Square
DEMOGRAPHICS							
Age	55.15 (0.97)	73.94 (0.99)	74.21 (1.03)	74.73 (1.03)	14525 (3, 473)	<0.001	HY < HO = OMCI = OAD
Sex (women/men)	126/130	75/68	32/31	7/8	n.a.	n.s.	Chi-Sq: 0.469
Education	14.61 (2.48)	13.86 (2.99)	12.22 (2.41)	11.20 (1.78)	20.07 (3, 473)	<0.001	HY = HO > OMCI = OAD
MMSE ($n = 218$)	n.a.	28.91 (1.12)	28.07 (1.41)	24.13 (2.39)	90.02 (2, 215)	<0.001	HO > OMCI > OAD
NEUROPSYCHOLOGY							
Verbal memory: immediate recall ($n = 438$)	14.59 (3.16)	12.36 (3.47)	10.35 (3.46)	7.5 (3.50)	31.7 (3, 434)	<0.001	HY > HO > OMCI > OAD
Verbal memory: delayed recognition ($n = 438$)	7.93 (2.27)	6.91 (2.35)	5.81 (2.50)	4.0 (2.63)	14.5 (3, 434)	<0.001	HY = HO > OMCI > OAD
DST ($n = 438$)	53.94 (9.33)	44.15 (9.51)	36.11 (8.73)	25.8 (8.94)	72.4 (3, 434)	<0.001	HY > HO > OMCI > OAD
D2 ($n = 432$)	164.45 (32.06)	136.79 (33.08)	105.67 (33.93)	76.67 (43.37)	50.1 (3, 428)	<0.001	HY > HO > OMCI > OAD
Finding similarities ($n = 439$)	26.64 (4.17)	26.77 (4.07)	22.6 (6.27)	16.0 (6.62)	18.1 (3, 435)	<0.001	HY = HO > OMCI > OAD
Verbal fluency ($n = 439$)	32.38 (9.36)	32.15 (8.23)	24.47 (8.48)	18.8 (8.9)	11.0 (3, 435)	<0.001	HY = HO > OMCI > OAD
Visuospatial thinking ($n = 437$)	25.41 (6.04)	21.79 (5.72)	17.53 (7.41)	11.56 (6.93)	24.2 (3, 433)	<0.001	HY > HO > OMCI > OAD
NSS	2.46 (1.97)	2.84 (1.91)	3.0 (1.96)	5.6 (3.11)	8.0 (3, 473)	<0.001	HY = HO = OMCI < OAD

MCI, mild cognitive impairment; AD, Alzheimer's disease; MMSE, mini-mental state examination; DST, digit symbol test; D2, D2-test; NSS, neurological soft signs; n.a., not applicable; n.s., not significant.

In the subtests, verbal memory recognition, verbal fluency, and finding similarities, significant group differences were found only between MCI and AD, while healthy young controls and healthy old controls showed similar results. AD patients demonstrated significantly more NSS compared to the other three subgroups. As demonstrated in **Figure 1** across all diagnostic groups, NSS scores were inversely correlated with years of school education ($r = -0.25$; $p < 0.001$). The ANCOVA with years of school education as a covariate [$F(4,472) = 15.78$, $p < 0.0001$] yielded a significant main effect (type III ss) of diagnostic group on NSS scores [$F(3,473) = 7.95$, $p < 0.0001$].

To further analyze the correlations between NSS and neuropsychology deficits, the subgroups of patients with MCI and AD were collapsed. Within this joint group of cognitively impaired, NSS scores were significantly inversely correlated with scores on the MMSE, on the DST, and on the tests for visuospatial functioning and verbal fluency, processing speed, and cognitive flexibility, respectively (**Table 2**).

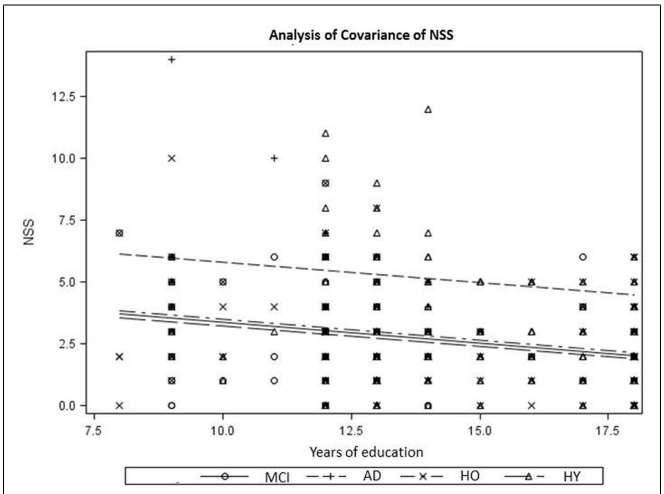


FIGURE 1 | NSS and years of education across diagnostic subgroups. NSS, neurological soft signs; HO, healthy old controls; HY, healthy young controls; MCI, patients with MCI; AD, patients with Alzheimer's disease.

DISCUSSION

The main findings of the present study can be summarized as follows: significantly increased NSS scores (i) were found in patients with AD but not in patients with MCI or healthy old controls compared to healthy young controls, (ii) correspond to deficient executive functioning and visuospatial apraxia and can be partially compensated for by cognitive reserve, and (iii), are not the sequelae of aging *per se*.

The present study confirmed increased NSS scores in patients with mild AD as previously described by a number of studies (2, 25, 26), which also examined patients in more advanced stages of the disease. This increase was not observed patients with MCI. In contrast, Li et al. (1) reported significantly increased NSS scores – which particularly involved motor coordination signs – in 29 MCI patients who were compared with 28 healthy controls. This discrepancy might refer to methodological differences, such as sample size and mode of recruitment, as well as the relatively greater severity of cognitive deficits in their MCI group, in particular (mean MMSE scores: 26.07 ± 2.33 vs. 28.07 ± 1.41, respectively).

Similar to the study of Chan et al. (27), NSS scores were significantly correlated with neuropsychological deficits involving executive functioning (verbal fluency, digit symbol test) and

Table 2 | Neuropsychological correlates of NSS in patients with MCI or AD.

NP-test	MMSE	Verbal memory (immediate recall)	Verbal memory (delayed recognition)	DST	D2-test	Finding similarities	Verbal fluency	Visuospatial thinking
NSS								
r uncorrected	***r* = −0.45****	*r* = −0.08	*r* = −0.03	***r* = −0.37***	*r* = −0.13	*r* = −0.21	***r* = −0.37***	***r* = −0.41****
(corrected)		(*r* = −0.04)	(*r* = −0.03)	**(*r* = −0.39*)**	(*r* = −0.15)	(*r* = −0.18)	**(*r* = −0.37*)**	**(*r* = −0.36*)**

Values corrected for education in brackets. Bold font indicates significant correlations.

NP, neuropsychology; MCI, mild cognitive impairment; AD, Alzheimer's disease; MMSE, mini-mental state examination; DST, digit symbol test; D2, D2-test; NSS, neurological soft signs.

**p < 0,005; **p < 0.001.*

visuospatial thinking. Verbal memory was not associated with NSS. In the light of these findings, the significant correlation of NSS and logical memory reported by Chan et al. (27) may refer to the fact that the latter also involves some aspects of executive functioning in the sense of mnestic strategies. It is notable that similar associations between NSS and executive deficits were also reported in schizophrenia [for review see Ref. (7)] and in HIV associated neurocognitive disorders (28). That motor performance in AD is related to executive functioning is further supported by the results of dual-task studies, which even yielded interactions between fall risk and executive dysfunctions (29–32).

In all subgroups under investigation, NSS were inversely related with years of school education as a marker of cognitive reserve. This association corresponded to a wealth of studies [for review see Ref. (11)], which identified motor abilities to be a protective factor for cognitive decline and could be mediated by the beneficial effects of aerobic exercise on the hippocampus (33) and the frontal cortices (34).

Despite the large sample size, a comparison of NSS scores between healthy young controls and healthy old controls yielded only minor, non-significant differences. In contrast, Chan et al. (27) who examined 180 subjects aged 60–96 suggested that NSS were very common among the elderly. Their study, however, differs with respect to a variety of important methodological details from the present investigation, among them the definition of cognitively intact controls by a MMSE score of >24. This definition may well have led to the inclusion of patients with mild AD who often showed MMSE scores up to 26. Along with this, educational levels were in the range of 6.8 ± 4.4 years and do not compare with the respective value found in our sample. Similarly, Kodama et al. (35) found deficits in diadochokinesis, finger-to-nose test, and tandem gate to increase with age in 348 subjects aged 60–89. However, educational level and MMSE scores were considerably lower than in our birth cohorts rendering a direct comparison of the results difficult. Therefore, our finding only applies to the rather "young" old investigated here and needs to be confirmed in the further course of the ILSE when subjects have reached a higher age.

Another important methodological limitation of our study involves the fact that only motor NSS were examined. Motor NSS are generally considered to be of particular importance (5) and can be easily applied (2). Likewise, Kodama et al. (35) demonstrated significant age effects only for the motor NSS cited above and vibration sense of the lower limbs but not for other sensory NSS.

As hypothesized, our investigation of two large birth cohorts confirmed increased NSS scores in patients with mild AD but not patients with MCI. According to our findings, NSS do not appear to be the sequelae of healthy aging since the two birth cohorts examined showed only minor, non-significant differences with respect to NSS. That NSS were found to be significantly associated with executive dysfunction corresponds to earlier studies in patients with schizophrenia. However, NSS are not only a marker of brain damage in AD but also reflect aspects of cognitive reserve. Longitudinal studies are necessary to establish the stability of NSS in aging, their prognostic value in MCI and – ultimately – to determine norm values for NSS. From a clinical standpoint, NSS should be considered as a reliable and easy to administer tool in the routine examination of patients with cognitive decline.

ACKNOWLEDGMENTS

The ILSE was supported in part by the Dietmar-Hopp-Foundation/St. Leon-Rot, Germany. PT was supported by Comisión Nacional de Investigación Científica y Tecnológica de Chile (CONICYT) through Fondo Nacional de Desarrollo Científico y Tecnológico (FONDECYT) project no. 11121301. We acknowledge the financial support of the Deutsche Forschungsgemeinschaft and Ruprecht-Karls-Universität Heidelberg within the funding programme Open Access Publishing. We are grateful to Dr. Phil. Franz-Josef Geider for statistical consulting.

REFERENCES

1. Li HJ, Wang PY, Jiang Y, Chan RCK, Wang HL, Li J. Neurological soft signs in persons with amnestic mild cognitive impairment and the relationships to neuropsychological functions. *Behav Brain Funct* (2012) **8**:29. doi:10.1186/1744-9081-8-29
2. Seidl U, Thomann PA, Schröder J. Neurological soft signs in nursing home residents with Alzheimers' disease. *J Alzheimers Dis* (2009) **18**:525–30. doi:10.3233/JAD-2009-1159
3. Bombin I, Arango C, Buchanan RC. Significance and meaning of neurological signs in schizophrenia: two decades later. *Schizophr Bull* (2005) **31**(4):962–77. doi:10.1093/schbul/sbi028
4. Schröder J, Niethammer R, Geider FJ, Reitz C, Binkert M, Jauss M, et al. Neurological soft signs in schizophrenia. *Schizophr Res* (1992) **6**:25–30. doi:10.1016/0920-9964(91)90017-L
5. Jahn T, Hubmann W, Karr M, Mohr F, Schlenker R, Heidenreich T. Motoric neurological soft signs and psychopathological symptoms in schizophrenic psychoses. *Psychiatry Res* (2006) **142**:191–9. doi:10.1016/j.psychres.2002.12.003
6. Schröder J. Soft signs, neuroleptic side effects, and schizophrenia. *Psychiatr Ann* (2003) **33**(3):214–20. doi:10.3928/0048-5713-20030301-10
7. Chan RCK, Wang Y, Wang L, Chen EYH, Manschreck TC, Li Z, et al. Neurological soft signs and their relationships to neurocognitive functions: a re-visit

with the structural equation modeling design. *PLoS One* (2009) **4**(12):e8469. doi:10.1371/journal.pone.0008469
8. Chan RCK, Xu T, Heinrichs RW, Yu Y, Wang Y. Neurological soft signs in schizophrenia: a meta-analysis. *Schizophr Bull* (2010) **36**(6):1089–104. doi:10.1093/schbul/sbp011
9. Mohr F, Hubmann W, Albus M, Franz U, Hecht S, Scherer J, et al. Neurological soft signs and neuropsychological performance in patients with first episode schizophrenia. *Psychiatry Res* (2003) **121**(1):21–30. doi:10.1016/S0165-1781(03)00203-8
10. Schröder J. Subsyndrome der chronischen schizophrenie. *Untersuchungen mit bildgebenden Verfahren zur Heterogenität schizophrener Psychosen.* Berlin: Springer-Verlag (1998). p. 43–9.
11. Sattler C, Erickson KI, Toro P, Schröder J. Physical fitness as a protective factor for cognitive impairment in a prospective population-based study in Germany. *J Alzheimers Dis* (2011) **26**(4):709–18. doi:10.3233/JAD-2011-110548
12. Dazzan P, Morgan KD, Orr KG, Hutchinson G, Chitnis X, Suckling J, et al. The structural brain correlates of neurological soft signs in AeSOP first-episode psychoses study. *Brain* (2004) **127**:143–53. doi:10.1093/brain/awh015
13. Thomann PA, Roebel M, Dos Santos V, Bachmann S, Essig M, Schröder J. Cerebellar substructures and neurological soft signs in first-episode schizophrenia. *Psychiatry Res* (2009) **173**:83–7. doi:10.1016/j.pscychresns.2008.07.006
14. Heuser M, Thomann PA, Essig M, Bachmann S, Schröder J. Neurological signs and morphological cerebral changes in schizophrenia: an analysis of NSS subscales in patients with first episode psychosis. *Psychiatry Res* (2011) **192**(2):69–76. doi:10.1016/j.pscychresns.2010.11.009
15. Zhao Q, Li Z, Huang J, Yan C, Dazzan P, Pantelis C, et al. Neurological soft signs are not "soft" in brain structure and functional networks: evidence from ALE meta-analysis. *Schizophr Bull* (2014) **40**(3):626–41. doi:10.1093/schbul/sbt063
16. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* (1975) **12**(3):189–98. doi:10.1016/0022-3956(75)90026-6
17. Oswald WD, Fleischmann VM. *Nürnberger-Alters-Inventar.* Erlangen-Nürnberg: Universität Erlangen-Nürnberg (1991).
18. Horn WC. *Leistungsprüfsystem.* Göttingen: Hogrefe (1983).
19. Schönknecht P, Pantel J, Kruse A, Schröder J. Prevalence and natural course of aging-associated cognitive decline in a population-based sample of young-old subjects. *Am J Psychiatry* (2005) **162**(11):2071–7. doi:10.1176/appi.ajp.162.11.2071
20. Oswald WD, Fleischmann VM. *Nürnberger Selbsteinschätzungsliste (NSL).* Erlangen-Nürnberg: Universität Erlangen-Nürnberg (1986).
21. Wittchen HU, Zaudig M, Schramm E, Spengler P, Mombour W, Klug J, et al. *SKID: Strukturiertes Klinisches Interview für DSM-III-R.* Göttingen: Beltz-Test (1991).
22. Schröder J, Kratz B, Pantel J, Minnemann E, Lehr U, Sauer H. Prevalence of mild cognitive impairment in an elderly community sample. *J Neural Transm Suppl* (1998) **54**:51–9. doi:10.1007/978-3-7091-7508-8_5
23. Levy R. Aging-associated cognitive decline. *Int Psychogeriatr* (1994) **6**(1):63–8. doi:10.1017/S1041610294001626
24. McKhann G, Drachmann D, Folstein M, Katzmann R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA work group under the auspices of the department of health and human services task force on Alzheimer's disease. *Neurology* (1984) **34**:939–65. doi:10.1212/WNL.34.7.939
25. Lam LL, Lui VWC, Chiu HFK. Associations between neurological soft signs and clinical progression Alzheimer's disease. *Hong Kong J Psychiatry* (2005) **15**:43–9.
26. Lautenschläger NT, Wu JS, Laws SM, Almeida OP, Clarnette RM, Joesbury K, et al. Neurological soft signs are associated with APOE genotype, age and cognitive performance. *J Alzheimers Dis* (2005) **7**(4):325–30.
27. Chan RCK, Xu T, Li HJ, Zhao Q, Liu HH, Wang Y, et al. Neurological abnormalities and neurocognitive functions in healthy elderly people: a structural equation modeling analysis. *Behav Brain Funct* (2011) **7**:32. doi:10.1186/1744-9081-7-32
28. Inostroza F, Valenzuela D, Schröder J, Toro P. [Neurological soft signs in HIV-infection and healthy controls – a clinical marker of cerebral damage]. *Revista chilena de neuropsiquiatria* (2014) **52**(2):121.
29. Beauchet O, Dubost V, Herrmann F, Rabilloud M, Gonthier R, Kressig RW. Relationship between dual-task related gait changes and intrinsic risk factors for falls among transitional frail older adults. *Aging Clin Exp Res* (2005) **17**(4):270–5. doi:10.1007/BF03324609
30. Lundin-Olsson L, Nyberg L, Gustafson Y. "Stops walking when talking" as a predictor of falls in elderly people. *Lancet* (1997) **349**:617. doi:10.1016/S0140-6736(97)24009-2
31. Lundin-Olsson L, Nyberg L, Gustafson Y. Attention, frailty, and falls: the effect of a manual task on basic mobility. *J Am Geriatr Soc* (1998) **46**:758–61.
32. Bloem BR, Steijns JAG, Smits-Engelsman BC. An update on falls. *Curr Opin Neurol* (2003) **16**:15–26. doi:10.1097/00019052-200302000-00003
33. Erickson KI, Voss MW, Prakash RS, Basak C, Szabo A, Chaddock L, et al. Exercise training increases size of hippocampus and improves memory. *Proc Natl Acad Sci U S A* (2011) **108**(7):3017–22. doi:10.1073/pnas.1015950108
34. Colcombe SJ, Erickson KI, Scalf PE, Kim JS, Prakash R, McAuley E, et al. Aerobic exercise training increases brain volume in aging humans. *J Gerontol A Biol Sci Med Sci* (2006) **61**(11):1166–70. doi:10.1093/gerona/61.11.1166
35. Kodama T, Nakagawa M, Arimura K, Koriyama C, Akiba S, Osame M. Cross-sectional analysis of neurological findings among healthy elderly: study in a remote island in Kagoshima, Japan. *Neuroepidemiology* (2002) **21**:36–43. doi:10.1159/000048612

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Received: 26 November 2014; accepted: 22 January 2015; published online: 11 February 2015.

Citation: Urbanowitsch N, Degen C, Toro P and Schröder J (2015) Neurological soft signs in aging, mild cognitive impairment, and Alzheimer's disease – the impact of cognitive decline and cognitive reserve. Front. Psychiatry ***6****:12. doi: 10.3389/fpsyt.2015.00012*

This article was submitted to Schizophrenia, a section of the journal Frontiers in Psychiatry.

frontiers

EPFL Innovation Park · Building I · 1015 Lausanne · Switzerland
T +41 21 510 17 00 · info@frontiersin.org · frontiersin.org