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Abstract

GOAL - The aim of this study is to assess to what extent psychomotor assessment can aid the clinician in differentiating between schizophrenia and other psychotic disorders

METHODS - Enrolled subjects were currently stabilized patients (n=304), who all met DSM-IV (APA, 2013) criteria for either schizophrenia (Sz; n=117), schizoaffective disorder (SaD; n=36), psychotic disorder not otherwise specified (P-NOS) (n=86), substance/medication-induced psychotic disorder (SIPD; n=33) or major depressive disorder with psychotic features (MDD-p; n=32). The patients were submitted to a psychomotor test battery.

RESULTS - Patients with schizophrenia generally perform worse on most tests. Using cluster analysis a combination of three tests, namely the sensory integration subscale of the neurological evaluation scale (NES), a figure copying task (FCT) and the finger tapping test (FTT), came out to be useful to clinically differentiate between schizophrenia and substance-induced psychotic disorder (SIPD) or psychosis not otherwise specified (P-NOS). When comparing schizophrenia only to a group of patients with SIPD, the differentiation potential becomes even greater with a 76.1% chance to correctly diagnose patients with schizophrenia and 75% chance for patients with SIPD.

CONCLUSION - A combination of NES, FCT and FTT shows promising results as a clinical tool in daily practice to differentiate schizophrenia from other psychotic disorders. Future prospective studies to confirm these results are necessary.

Key words: psychotic disorder, schizophrenia, substance-induced psychotic disorder, psychosis not otherwise specified, psychomotor, neurological soft signs

1. Introduction

Schizophrenia is a severe psychiatric disorder which affects about 1% of the population and is characterized by positive, negative, cognitive and psychomotor symptoms. Psychomotor symptoms such as psychomotor slowing, neurological soft signs, diminished activity and catatonic symptoms (Docx et al., 2012; Walther et al., 2009; Walther & Strik, 2012; Morrens et al. 2014) are present irrespective of antipsychotic treatment (Peralta et al., 2010, 2011) and have been demonstrated to be predictive for functional and clinical outcome (Morrens et al., 2007).

Schizophrenia is part of what sometimes is considered as a spectrum of psychotic disorders including schizoaffective disorder, mood disorders with psychotic features and substance induced psychosis (Mørch et al., 2016). Importantly, the phenotypical presentation of these illnesses may be very similar, especially in the acute phase when psychotic features dominate the clinical symptomatology. As pharmacological therapeutical strategies can differ substantially between different psychosis spectrum disorders, difficulties in making

differential diagnoses gravely endanger adequate patient treatment. An easy to use tool that aids the clinician in the diagnostical process would thus be of value.

More stable schizophrenia-related deficits as cognitive and motor symptoms might prove an interesting strategy towards correct differentiation in diagnosis. However, only a handful of studies (Stip et al., 2005; Patiny et al., 2015) explored the relevance of these symptoms as diagnostical tools. Stip and colleagues (2005) compared schizophrenic and schizoaffective patients on cognitive and motor symptom assessment and demonstrated that these disorders mainly differed in patient performance on a motor task of the Cambridge Neuropsychological Test Automated Battery (CANTAB). Gorynia and colleagues (2003) compared performance on a finger tapping test of schizophrenic patients to that of patients with schizoaffective disorder and substance-induced psychosis and healthy controls. They found schizophrenia patients to have significantly lower scores than all three other comparison groups and suggested that the tool may have a place in the clinical investigation of acute psychotic inpatients. Along this line, Rigucci et al. (2014) were able to discriminate schizophrenia from bipolar disorder using neurological soft signs (NSS). Neurological soft signs contain deficits in sensory integration, motor coordination and motor sequencing (Morrens et al. 2007). Finally, Kruger and colleagues (2003) clearly showed differential catatonic presentations between schizophrenia, mania, mixed mania and major depression. As such, the motor syndrome thus could contribute in differentiating schizophrenia from other psychotic disorders.

In the present study, the performance of schizophrenic patients on a psychomotor test battery will be compared to that of patients with other psychotic disorders (schizoaffective disorder, major depressive disorder with psychotic features, substance induced psychosis and psychosis not otherwise specified). We will evaluate to what extent psychomotor assessment can aid the clinician in differentiating schizophrenia from other psychotic disorders.

2. Methods

2.1. Participants

Enrolled subjects were *recent in remission* patients with a psychotic disorder (n=304). All patients met DSM-IV (APA, 2013) criteria for either schizophrenia (Sz; n=117), schizoaffective disorder (SaD; n=36), psychotic disorder not otherwise specified (P-NOS) (n=86), substance/medication-induced psychotic disorder (SIPD; n=33) or major depressive disorder with psychotic features (MDD-p; n=32). *In the total dataset, 22 bipolar patients were included. Nevertheless, this sample consisted of several subgroups depending on illness phase (manic, depressed, mixed episode, with/without psychotic features). As none of these groups were large enough to enter analyses (all n<6), we chose to omit bipolar patients from the analyses*

Patients were recruited from the University Department of Psychiatry, Campus Psychiatric Hospital Duffel, Duffel, Belgium. All patients entering the hospital were tested within 5 weeks after admission, when *remission* of the psychotic episode was reached. *All motor assessments were performed by the same person (HM). Diagnosis was made based on a semi-structured interview by the psychiatrists attached to the unit (FV, MM).* Patients underwent psychomotor assessment as part of standardized clinical care. Data were

analyzed retrospectively. The study was approved by the ethical committee of the University hospital of Antwerp.

2.2. Psychomotor tasks

2.2.1. The Neurological Evaluation Scale (NES)

The NES (Buchanan and Heinrichs, 1989) is a frequently used instrument for the assessment of neurological soft signs (NSS), which examines 26 of these signs. A validated dutch translation of the NES (NES-d) was used. The scale generates three subscales: sensory integration (NES-SI), motor coordination (NES-MC) and motor sequencing (NES-MS). NES-SI includes audiovisual integration, stereognosis, graphesthesia, extinction and right/ left confusion. The NES-MC subscale includes the following items: tandem walk, rhythm tapping parts A and B, and finger-thumb opposition. Finally, NES-MS includes the fist-ring, fist- edge-palm and Ozeretski tests. Total scores of these subscales were used as severity measures.

2.2.2. Finger Tapping test (FTT)

The Finger Tapping Test, a simple but well validated tool to assess psychomotor speed, was administered according to its conventional protocol (Reitan&Wolfson, 1993). The tasks yields two separate scores for both the dominant (FTT-d) and the non-dominant hand (FTT-nd).

2.2.3. Copying tasks

The Line Copying Task (LCT; Bervoets et al., 2014; Docx et al., 2013) is a computerized copying task developed by our lab, which was designed to delineate slowing in the initiation of movement from slowing in the execution of movement. The stimuli used in this task are simple, straight lines that can be oriented in four directions (vertical, horizontal, and diagonal in both directions). The participant is asked to copy these lines as fast as possible on a sheet of paper divided in 3 by 4 cm squares and placed on a digitizer. Stimulus presentation starts as soon as the participant touches the 'start' circle with the digitized pen and ends when the participant starts drawing the line. The task consists of 24 trials.

The outcome measures used are initiation time (IT), being the time between the stimulus presentation and the start of the first drawing movement, and execution time (ET), the time the participant is actually drawing. This task has been used in our research group since the mid 90s in numerous studies investigating the symptomatology and pathogenesis of motor disturbances in schizophrenia, mood disorders, substance use disorders, and eating disorders.

The Figure Copying Task (FCT; Morrens et al., 2008, Docx et al., 2014) is another task that is assessed according to the same protocol as the LCT. The FCT offers 12 stimuli to be copied, consisting of three types of figures: letters, familiar figures and unfamiliar patterns.

Similar to the LCT, variables are the initiation time (FCT-IT) and the execution time (FCT-ET). Additionally, the reinspection time (FCT-REIN) is also calculated, which refers to the time the subjects take to reinspect the stimulus, by replacing the pen in the start circle, which made the stimulus reappear on the screen. The mean average velocity while completing the figure was also calculated (FCT-v).

2.2.4. Stereotypy test apparatus

The stereotypy test apparatus (STA; Hoffman et al., 2003; Morrens et al., 2006) is a device

featuring nine randomly distributed buttons. The test comprises 200 trials in each of which the subjects need to press one of the buttons with their index finger after an acoustic signal (1/s) while applying the most random order possible. Whereas redundancy, i.e. the complement of relative entropy, is represented by the chance of total chaotic randomness, redundancy of context (STA-RC) is used as a measure for stereotypy (Guttmann and Kranner, 1960). A STA-RC score of 0.000 denotes a perfectly random response or the complete absence of any pattern, and 1.000 the presence of a fixed repetitive response pattern and thus a lack of randomness.

2.3. Statistical analyses

The software package SPSS 23.0 was used for the statistical analyses.
Multivariate analyses were used to compare the patient groups in their psychomotor performance, cith contrast analyses comparing schizophrenia to other diagnostical groups. In order to evaluate whether psychomotor performance could differentiate schizophrenia from other patient groups, we used hierarchical cluster analyses (Ward's method). All significant variables from the multivariate GLM analysis (see table 2) entered the cluster analysis (single solution, predefined number of clusters n=5). Non-parametric correlations were calculated using Spearman's rho.

3. Results

3.1. Demographic variables

Demographic variables of the five patient groups are presented in Table 1. Significant group differences were present for sex, age and duration of illness (DOI; defined as time between the start of illness as determined by the first admission in a psychiatric hospital and psychomotor assessment). All patient groups were matched for study level, weight and chlorpromazine (CPZ) equivalents of antipsychotic treatment. Age differences were driven by significant differences between schizoaffective disorder group on one hand and schizophrenia (p=.008) and SIPD group (p=.013) on the other. Post-hoc analyses only reveal a significant difference between schizoaffective and SIPD group (p=0.019) for DOI. As can be expected, the MDD group were significantly more treated with antidepressants compared to other groups.

-- INSERT TABLE 1 ABOUT HERE--

3.2. Psychomotor performance in the psychotic patient groups

All 5 patient groups entered a multivariate GLM, with contrast analyses comparing all patient groups to the schizophrenic group, while controlling for age, sex, CPZ equivalents and DOI ($F=1.378$; $p = .048$). In this multivariate analysis, sex ($F=5.541$; $p < .001$) and age ($F=1.986$; $p=.027$) had a significant effect, which was mirrored in the effect of DOI that almost reached significance ($F=1.664$; $p=.076$). CPZ equivalents equally almost reached significance ($F=1.652$; $p=.079$), whereas the use of antidepressants did not ($F<1$).

-- INSERT TABLE 2 ABOUT HERE --

In concurrent contrast analyses (see also table 2) schizophrenic patients performed significantly worse on the NES-SI compared with all other groups (SA p=.017; P-NOS p=.003; SIP p=.001)) with exception of the PD group.
The other NES symptom clusters were marginally more present in schizophrenia compared to SA patients (MC: p=.031); MS: p=.075) but not compared to other groups. The FTT of the non-dominant hand was significantly worse in schizophrenia compared with the SA group (p=.015) but not with other groups.
Schizophrenic patients were significantly slower in initiation times on the LCT (p=.015) and the FCT (p=.036) than the SIP group but not to other patient groups. Similarly, execution times were slower in schizophrenia patients on the LCT (p=.007) and the FCT (p=.002) compared to the SIPD group, and additionally also in the more demanding FCT (but not the LCT) compared to the P-NOS group (p=.018). This was mirrored in a slowed average drawing speed in the schizophrenic group on the FCT compared to the SIPD (p<.001) groups. Schizophrenic patients also reinspected more in the FCT than the SIPD (p=.011) and the P-NOS (p=.010) groups.
Finally, schizophrenic patients performed marginally worse than their schizoaffective peers on the stereotypy test apparatus (p=.057) but not compared to other groups.

3.3. Can we use the psychomotor assessments to differentiate between schizophrenia and other psychotic disorders?

In order to evaluate whether psychomotor performance could differentiate schizophrenia from other patient groups, we used hierarchical cluster analyses (Ward's method). All significant variables from the multivariate GLM analysis (see table 2) entered the cluster analysis (single solution, predefined number of clusters n=5). Disappointingly, he cluster attributed to each patient correlated only mildly with the actual diagnosis (Spearman's rho = 0.202, p=.001).

In follow-up analyses, the schizophrenia group entered analyses with each of the other diagnostical psychosis groups separately. Interestingly, when only the schizophrenia and the SIPD patients entered a second cluster analysis (single solution, predefined number of clusters n=2) with the same selection of psychomotor measures, cluster membership correlated much higher with actual diagnosis (Spearman's rho = .458, p<.001) and 75.0% of the schizophrenic patients and 77.8.0% of the SIP group were each appointed to a separate cluster.

When schizophrenic and P-NOS patients were included in a similar method, only a mild correlation was found (Spearman's rho = .193; p=.012). Of the schizophrenic patients, 77.2% of the patients were correctly identified as such based on the psychomotor battery. However, only 59.2% P-NOS patients were correctly attributed to the same cluster.

When schizophrenic peers were compared to their schizoaffective peers, the cluster attributed to each patient group did not correlate with actual diagnosis. Similarly, with schizophrenic and psychotic depressed patients entering analyses, again, no significant correlations between cluster attribution and diagnosis was found.

4. Discussion

Patients with schizophrenia generally performed worse on most psychomotor tests compared to other psychotic disorders. Cluster analysis shows that a combination of psychomotor tests, can be used to clinically differentiate between schizophrenia on one hand and substance induced psychosis on the other hand as the battery had a 75% chance of correctly diagnosing patients with schizophrenia and 77.8% chance for patients with SIPD. To a lesser degree, schizophrenia patients demonstrated a differential response profile compared to patients with psychosis NOS, although a substantial overlap was seen. The psychomotor battery was not able to distinguish schizophrenia patients from schizoaffective and psychotic depressed patients. *It is worth mentioning that no absolute differences in the clinical psychomotor presentation were found when comparing the different diagnostical groups within the psychosis spectrum. Nevertheless, clear statistical differences were found between the spectrum's poles (schizophrenia on one hand and substance-induced psychotic disorder or psychotic disorder NOS on the other), thus making psychomotor testing helpful to aid the clinician in differentiating between psychotic disorders.*The current findings are thus in line with these previous studies in demonstrating that clinical tools assessing psychomotor functioning in psychotic patients can be a real aid in daily clinical practice to increase diagnostical accuracy.

Whereas Kraepelin and Bleuler, the earliest describers of the illness, defined psychomotor features as important disease symptoms, contemporary clinicians tend to have a strong focus on positive psychotic symptoms, a shift that has partially been explained by the introduction of antipsychotics in the 1950s (Morrens et al., 2007). But as stated before, positive symptoms alone are often insufficient to correctly diagnose patients in acute inpatient settings (Owoeye et al. 2013). *Psychomotor symptoms are typically unrelated to the psychotic symptom cluster (Morrens et al. 2007) and only inconsistent moderate associations are found with negative symptoms (Henkel et al. 2004; Morrens et al. 2007) and cognitive symptoms (Docx et al. 2012). Therefore, one could argue the psychomotor syndrome to be another independent symptom dimension within the psychosis spectrum.*

In daily clinical practice differentiating between schizophrenia and substance induced psychosis is often difficult, especially in patients with recent onset of psychosis since positive psychotic signs and symptoms are much alike in both disorders. Moreover, up to 47% of patients suffering from schizophrenia have a reported comorbidity of substance abuse at some point during their lifetime (Regier et al. 1990). However, it is important to differentiate between the two diagnoses as practice guidelines for the treatment of substance abuse related psychosis and those for the treatment of schizophrenia tend to differ substantially (McIver et al., 2006; Lehman et al., 2010). Our results show that psychomotor assessments may contribute to that clinical process.

Similarly, schizophrenia is also difficult to differentiate from psychosis not otherwise specified (P-NOS). Patients with P-NOS are a very heterogenic group as there are no pathognomic features. As a result, the diagnostic stability of this P-NOS is very low. In Fusar-Poli et al. (2016) only one third of the patients who were initially diagnosed with P-NOS retained the initial diagnosis whereas an equal portion of patients shifted towards schizophrenia. Mean follow-up in this meta-analysis was only 4.5 years so possibly the

diagnostic stability of this diagnosis over a long term period is even lower. This is reflected in our data as the psychomotor battery could not reliably differentiate between schizophrenia and P-NOS although the psychomotor test battery did distinguish between the two groups to some degree. When looking at the differentiation between schizophrenia and schizoaffective disorder, Stip and colleagues (2005) found motor screening (MOT) and paired associates learning task (PAL) to be the best differentiator between these two diagnoses with schizoaffective patients performing better. *Boks et al. (2004) found the movement disorder dimension of NSS to be specific to schizophrenic patients when compared to patients with mood disorders. Similar findings were shown in Verkatasubramaian et al. (2003) where never-treated schizophrenic patients had significantly more neurological soft signs. Dazzan et al. (2008) found NSS to be specific to the presence of psychosis in general. However, these were not in line with our findings as the psychomotor battery could not differentiate between these schizophrenia and depressed patients in our sample.*

There are some limitations to this study. First, the severity of psychosis was not taken into account as clinical symptom scores for psychotic features were not available for all patients. Second, all patients were hospitalized in an acute psychiatric setting. Therefore, conclusions about psychomotor functioning in patients with psychotic disorders in remission can not be made. *Last, although the person responsible for the psychomotor assessment was not strictly blinded for diagnosis, and thus a bias cannot be ruled out, we expect this effect to be minimal, as most of these scores were computer- or device-generated.*

To conclude, a combination of psychomotor assessment tools was shown a useful aid in differentiating schizophrenia from SIPD and to a lesser degree from P-NOS. As such, psychomotor assessment shows promise in helping the clinician adequately differentiate between these illnesses from a diagnostical point of view in daily practice. Future research should evaluate in a prospective study whether this proposed psychomotor battery indeed has predictive validity towards diagnosis in a psychiatric admission setting. *Future research should also evaluate the potential benefit of other motor measures, inlcuding intruments for bradykynesia or tremor, rating scales (e.g. Bush Francis Catatonia Rating Scale, Salpetriere Retardation Rating scale,…) or actigraphic assessments of sponaneous motor behavior.*

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Table 1: Demographic Variables

	Schizophrenia (n=117)	Schizo-affective disorder (n=36)	Psychosis not otherwise specified(n=86)	Substance induced psychotic disorder (n=33)	Major depressive disorder with psychotic features (n=32)	Test
Sex (M,%)	68 (58%)	17 (47%)	54 (63%)	27 (82%)	13 (41%)	P=.007*
Age (age, SD)	32,2 (10,4)	37,2 (12,2)	34,6 (12,9)	29,6 (9,5)	40,5 (14,4)	F=3,64$^{O,+}$ (p=0.007)
Weight	72,7 (14,0)	73,9 (16,7)	76,9 (15,5)	74,3 (13,8)	75,5 (14,3)	F=.913 ^{O} (NS)
Study level						P=.208*
Primary education	40(34%)	12 (33%)	29 (34%)	16 (49%)	8 (25%)	
Secondary education	57 (49%)	18 (50%)	39 (45%)	14 (42%)	15 (47%)	
Higher education	19 (16%)	6 (17%)	16 (19%)	3 (9%)	9 (28%)	
DOI, in months (mean, range)	112,8 (2-445)	132,9 (13-365)	88,8 (2-472)	60,3 (2-240)	100,8 (13-391)	F=3,26 ^{O,} # (p=.012)
CPZ (mean, SD)	465,4 (276,2)	483,3 (435,8)	380,4 (209,9)	391,6 (278,2)	378,3 (315,5)	F=1,803^{O} (NS)
Antidepressants (n, %)	24 (21%)	8 (22%)	22 (26%)	4 (12%)	19 (59%)	P<.001*

* = independent samples kruskal Wallis test

^{O} = Multivariate GLM analysis

+ = Post-hoc analyses (Bonferroni) demonstrate significant age differences between schizoaffective disorder group on one hand and schizophrenia (p=.008) and SIP group (p=.013) on the other. All other group comparisons are non-significant

= Post-hoc analyses only reveal a significant difference between schizoaffective and SIP group(p=0.019) for DOI

DOI = Duration of Illness, defined as time between first admission in psychiatric hospital and psychomotor assessment

CPZ = chlorpromazine equivalents

Table 2: Psychomotor test results (mean (SD)).

	Schizophrenia (n=116)	Schizoaffective disorder (n=36)	Psychosis NOS (n=86)	Substance induced psychosis (n=33)	Major depressive disorder with psychotic features (n=32)	F (p)
NES-SI	3.1 (2.1)	2.4 (1.3)	2.3 (1.7)	1.8 (1.8)	2.9 (1.7)	2,695 (.005) **
NES-MC	2.9 (1.9)	2.3 (1.3)	2.6 (1.8)	2.3 (1.5)	3.0 (2.1)	2,199 (.023) *
NES-MS	4.6 (2.9)	3.7 (1.9)	3.7 (2.7)	3.8 (2.5)	4.4 (2.3)	2.384 (.013) *
FTT-d	49.5 (7.8)	50.9 (7.4)	50.6 (10.4)	52.8 (7.1)	49.0 (9.7)	8.480 (<.001) ***
FTT-nd	45.3 (7.3)	46.9 (7.5)	46.7 (8.5)	49.4 (7.9)	43.3 (7.8)	11.215 (<.001) ***
LCT-IT (s)	.97 (.39)	.89 (.14)	.88 (.22)	.80 (.21)	.96 (.23)	3.436 (.001) ***
LCT-ET (s)	.47 (.23)	.46 (.14)	.42 (.19)	.33 (.17)	.46 (.25)	3.340 (.001) ***
FCT-IT (s)	1.55 (.63)	1.49 (.34)	1.48 (.48)	1.28 (.38)	1.54 (.44)	1.969 (.044) *
FCT-ET (s)	4.57 (2.33)	4.41 (1.28)	3.81 (1.39)	3.26 (1.31)	4.26 (1.27)	2.780 (.004) **
FCT-REIN (s)	.76 (.86)	.68 (.54)	.45 (.41)	.37 (.41)	.54 (.43)	1.706 (.088)
FCT-v						4.620 (<.001) ***
STA-RC	.26 (.124)	.23 (.099)	.23 (.10)	.25 (.13)	.26 (.13)	1.003 (.438)

* $p \leq .05$
** $p \leq .01$
*** $p \leq .001$

Abbreviations:
NES-SI: Neurological Evaluation Scale – Sensory Integration
NES-MC: Neurological Evaluation Scale – Motor Coordination
NES-MS: Neurological Evaluation Scale – Motor Sequencing
FTT-d: Finger Tapping Test- dominant hand
FTT-nd: Finger Tapping Test - non-dominant hand
LCT-IT: Line Copying Task – Initiation Time
LCT-ET: Line copying Task- Execution Time
FCT-IT: Figure Copying Task – Initiation Time
FCT-ET: Figure Copying Task – Execution Time
FCT-REIN: Figure Copying Task – reinspection time
FCT-v: Figure Copying Task – mean average velocity
STA-RC: Stereotypy Test Apparatus - Redundancy of Context