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Profiling cognitive impairment in treatment-resistant schizophrenia patients

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ABSTRACT

The aim of this study was to compare cognitive performance between schizophrenia patients with and without treatment resistance (TRS and non-TRS patients) taking into account psychopathological symptoms and antipsychotic treatment. The following cognitive tests were administered to 53 TRS patients and 32 non-TRS subjects: Rey Auditory Verbal Learning Test (RAVLT), Trail Making Tests (TMT-A and TMT-B), verbal fluency tests (FAS test and Supermarket), as well as selected Wechsler Adults Intelligence Scale (WAIS-R-PI) subtests: Digit Symbol Coding Test, Digit Span Forward and Backward and Similarities. TRS patients performed significantly worse in comparison with non-TRS patients on the measures of processing speed (TMT-A, Stroop test, FAS test, Supermarket test, Digit Symbol Coding test), verbal fluency (FAS test, Supermarket test), cognitive flexibility and executive functions (Stroop test) after controlling for age, illness duration, clinical symptoms severity, the number of years of completed education and antipsychotics' dose. Cognitive performance was associated with negative and general symptomatology. Anticholinergic activity of antipsychotics had debilitating effect on cognitive functioning in non-TRS patients (FAS test) and in TRS patients (TMT-B test, Stroop test, RAVLT subtests, Digit Coding test and Similarities test), while low anticholinergic activity of antipsychotics was associated with better cognitive performance in non-TRS patients (Backward Digit Span test) and in TRS patients (Similarities test). Results of this study indicate that cognitive deficits are more robust in TRS patients than in non-TRS subjects, and are associated with clinical symptoms as well as the treatment with antipsychotics that exert high anticholinergic activity.

1. Introduction

Although great progress in the pharmacotherapy of psychotic disorders was achieved in the last three decades, about one-third of schizophrenia patients still experience persistent psychotic symptoms despite appropriate antipsychotic treatment (Elkis, 2007). The lack of response or poor response to antipsychotics by schizophrenia patients has been defined as treatment-resistant schizophrenia (TRS). Patients with TRS appear to have high rates of comorbid substance and alcohol use disorders, suicidal ideation and poor functional capacity (Kaneda et al., 2009; Kennedy et al., 2014). Moreover, it has been reported that there are several neuroimaging correlates associated with treatment resistance in schizophrenia (for review see Nakajima et al. (2015)). It has been shown that in comparison to non-TRS, TRS subjects have more widespread reduction in cortical thickness (Zugman et al., 2013) and lower dopamine synthesis capacity in striatum (Demjaha et al., 2012) as well as elevated glutamate levels in anterior cingulate cortex (Demjaha et al., 2014).

Poor functional outcome in schizophrenia is strongly associated with cognitive impairments, which are core clinical characteristics of schizophrenia observed in more than 80% of the patients (Keefe and Fenton, 2007). Interestingly, cognitive impairment occurs already in the premorbid period and it is still unsolved as to whether it progresses in the course of schizophrenia (Bora et al., 2010). Profiling cognitive functioning in schizophrenia has revealed pronounced impairments across several domains including current IQ, category fluency, verbal memory, sustained attention and response inhibition (Bora et al., 2010). There is no agreement as to which test is most specific to schizophrenia cognitive decline; however, a recent study showed that the Digit Symbol Coding test

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differentiates schizophrenia patients from control subjects better than widely used measures of episodic memory, executive functioning and working memory (Dickinson et al., 2007). Numerous rehabilitation programmes have been developed in order to alleviate the burden associated with cognitive decline in schizophrenia (La Paglia et al., 2013; Mak et al., 2013) since cognitive deficits poorly respond to antipsychotic treatment. Although there is evidence for a broader range of cognitive improvement observed in patients receiving second-generation antipsychotics than those treated with typical antipsychotic drugs (Hill, 2010), some reports do not confirm these findings (Tybura et al., 2013). In addition, cognitive performance might be worsened by the use of anticholinergic medications including antipsychotics exerting high anticholinergic activity (Tandon, 2011).

It has been proposed to include cognitive impairment and global functioning in definitions of TRS (Keefe and Fenton, 2007). However, studies in this field are scarce and thus do not support redefinition of TRS. To date, there is only one cross-sectional study profiling cognitive impairment in TRS patients (de Bartolomeis et al., 2013). Authors found that TRS patients have significantly lower scores on the Verbal Memory test from the Brief Assessment of Cognition in Schizophrenia (BACS) and poorer cognitive performance correlated with the severity of negative symptoms among TRS patients (de Bartolomeis et al., 2013).

In this study, we aimed at profiling cognitive deficits of TRS subjects in comparison to non-TRS patients and investigating the influence of antipsychotic pharmacotherapy on cognitive performance in schizophrenia. We hypothesised that (1) TRS patients might be characterized by more severe cognitive decline in comparison with non-TRS patients; (2) higher severity of psychopathological symptoms might be associated with more severe cognitive impairment in schizophrenia patients, and (3) the use of antipsychotics with higher anticholinergic activity might be associated with worse cognitive performance in patients with schizophrenia.

2. Methods

2.1. Subjects

We recruited 85 schizophrenia patients: 35 males (aged: 33.91 ± 9.98) and 50 females (aged: 39.22 ± 11.01). Schizophrenia was diagnosed by the same two senior board psychiatrists according to ICD-10 and DSM-IV criteria and confirmed using the Operational Criteria for Psychotic Illness (OPCRIT) checklist (McGuffin et al., 1991). Lifetime psychopathology and course of the disorder were also evaluated using the OPCRIT checklist, while current psychopathological manifestation was assessed using the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987), and Scales for Assessment of Positive and Negative Symptoms (SAPS and SANS) (Andreasen, 1982, 1990). All participants were Caucasians and came from the same geographic area – Lower Silesia, Poland. There were following inclusion criteria: a diagnosis of schizophrenia according to ICD-10 and DSM-IV criteria, at least one psychotic episode in the past and age above 18 years old. The patients were excluded if they had positive history of traumatic brain injury, neurologic disorders, comorbid drug and/or alcohol use disorders with exception of nicotine dependence and severe physical health impairments.

There were 32 non-TRS patients (males/females: 11/21) and 53 TRS subjects (males/females: 24/29) ($p > 0.05$). Non-TRS and TRS patients were matched for age and sex. Treatment resistance was defined based on little or no symptomatic response to at least 2 antipsychotic trials with different mechanisms of action and duration of at least 6 weeks that were used in therapeutic doses (Lehman et al., 2004).

Patients were treated with 13 different antipsychotic drugs (in the rank order): clozapine (27%), risperidone (20%), including long-acting injectable risperidone (1%) and oral solution (3%), olanzapine (15%), aripiprazole (8%), quetiapine (7%), ziprasidone (7%), haloperidol (4%), perazine (3%), levopromazine (2%), sulpiride (1%), sertindole (3%), amisulpride (1%) and zuclopenthixol (1%). Chlorpromazine equivalent doses were calculated according to the consensus described by Kroken et al. (2009). Twenty one patients were under combined antipsychotic treatment (5 non-TRS and 16 TRS). There were no significant differences between TRS and non-TRS patients with respect to the number of patients receiving first- or second-generation antipsychotics ($\chi^2 = 0.58$, $df = 1$, $p = 0.62$). Assuming a 150–600 mg/day dose-range of chlorpromazine equivalents as a reliable therapeutic range (Gardner et al., 2010), none of the antipsychotics were under-dosed neither in TRS nor in non-TRS patients.

The following tests were used for assessment of cognitive performance: Rey Auditory Verbal Learning Test (RAVLT), Trail Making Tests (TMT-A and TMT-B), verbal fluency tests including FAS letters test and Supermarket test, as well as selected Wechsler Adults Intelligence Scale (WAIS-R-PI) subtests including Digit Symbol Coding test, Digit Span Forward and Backward tests, and Similarities test. Not all patients were able to complete all cognitive tests.

2.2. Statistics

Differences in demographic and clinical variables between TRS and non-TRS patients were compared using the analysis of variance (ANOVA) (age, age of onset, number of years of completed education, illness duration, chlorpromazine equivalent, BMI, pack-year index) and χ^2 test (sex, education, mode of onset, premorbid work adjustment, premorbid social adjustment and premorbid personality disorder, family history of schizophrenia and course of the disorder). The comparison of TRS and non-TRS patients with respect to the severity of psychopathological symptoms (PANSS, SANS, SAPS) and cognitive performance was performed using ANOVA. The association between cognitive performance and psychopathology with chlorpromazine equivalents of antipsychotics with low and high anticholinergic activity was assessed using Pearson's correlation coefficient. The association between cognitive performance and chlorpromazine equivalent of drugs with low or high anticholinergic activity was assessed using Spearman's rank correlation coefficient. Correlations of cognitive performance with illness duration, PANSS subscales and chlorpromazine equivalent as well as correlations between smoking and PANSS subscales were tested using Pearson's correlation coefficient. Analysis of covariance (ANCOVA) was performed in order to assess differences in cognitive performance between TRS and non-TRS patients with respect to all applied cognitive tests after controlling for possible confounders, such as age, illness duration, psychopathological symptoms severity and chlorpromazine equivalent. Linear regression analysis was performed in order to estimate a degree of association between psychopathological symptoms severity and cognitive performance, adjusting for age, illness duration and chlorpromazine equivalent. Differences were considered as statistically significant if the p-value was less than 0.05 and trend-level significance was defined as the p-value between 0.05 and 0.1. Due to multiple comparisons, Bonferroni correction and partial Bonferroni correction were applied to the level of significance. The latter one takes into account mean correlations between studied variables (Gong et al., 2000). All analyses were performed using the Statistical Package for Social Sciences (SPSS) version 20.