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Neuropsychological profile in adult schizophrenia measured with the CMINDS

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ABSTRACT

Schizophrenia neurocognitive domain profiles are predominantly based on paper-and-pencil batteries. This study presents the first schizophrenia domain profile based on the Computerized Multiphasic Interactive Neurocognitive System (CMINDS®). Neurocognitive domain *z*-scores were computed from computerized neuropsychological tests, similar to those in the Measurement and Treatment Research to Improve Cognition in Schizophrenia Consensus Cognitive Battery (MCCB), administered to 175 patients with schizophrenia and 169 demographically similar healthy volunteers. The schizophrenia domain profile order by effect size was Speed of Processing ($d=-1.14$), Attention/Vigilance ($d=-1.04$), Working Memory ($d=-1.03$), Verbal Learning ($d=-1.02$), Visual Learning ($d=-0.91$), and Reasoning/Problem Solving ($d=-0.67$). There were no significant group by sex interactions, but overall women, compared to men, showed advantages on Attention/Vigilance, Verbal Learning, and Visual Learning compared to Reasoning/Problem Solving on which men showed an advantage over women. The CMINDS can readily be employed in the assessment of cognitive deficits in neuropsychiatric disorders; particularly in large-scale studies that may benefit most from electronic data capture.

1. Introduction

Patients with schizophrenia show significant cognitive deficits (Dickinson et al., 2007; Heinrichs and Zakzanis, 1998; Schaefer et al., 2013). These deficits are present in first-episode patients (Mesholam-Gately et al., 2009), non-ill relatives (Dickinson et al., 2007), and individuals at clinical (De Herdt et al., 2013; Giuliano et al., 2012) or genetic risk (Agnew-Blais and Seidman, 2013) for psychosis, suggesting that they are associated with disease liability and not merely a consequence of the disease or its treatment. Cognitive deficits among patients with schizophrenia have been associated with poorer functioning (Green et al., 2000; Green et al., 2004a) and hence may provide important treatment targets. This study assesses the schizophrenia neurocognitive domain profile based on the Computerized Multiphasic Interactive Neurocognitive System (CMINDS®; www.neurocomp.com), to determine its usability in large-scale studies of neuropsychiatric illness.

Neuropsychological test performance across cognitive domains (e.g., attention, working memory, verbal learning, etc.) is often

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presented as a cognitive domain profile (Saykin et al., 1991; Saykin et al., 1994). These profiles are created by normalizing scores using control means and standard deviations and grouping test scores to allow for visualization of putatively 'differential' deficits between cognitive domains. Many studies use different tests that have dissimilar discriminating power (Chapman and Chapman, 1973) within each of these cognitive domains, making comparisons of profiles across studies difficult. Meta-analyses on neuropsychological deficits in schizophrenia handle this issue by computing effect sizes based on individual test scores rather than on cognitive domain scores, which may vary in composition across studies (Dickinson et al., 2007; Schaefer et al., 2013).

The issue of variability in the composition of test batteries is of particular relevance with regard to the assessment and comparison of putative pro-cognitive treatments (Green et al., 2004b). To advance the development of such treatments, the National Institutes of Mental Health (NIMH) funded the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) initiative to develop a consensus cognitive battery for use in schizophrenia clinical trials (Kern et al., 2008; Nuechterlein et al., 2008). The MATRICS initiative (1) selected tasks based on reliability, repeatability, sensitivity to site effects, practicality, tolerability, and relationship to functional outcome, (2) put forward the MATRICS Consensus Cognitive Battery (MCCB) comprised of 6 cognitive domains – Speed of Processing, Attention/Vigilance, Working Memory, Verbal Learning, Visual Learning, and Reasoning/Problem Solving – and one domain of Social Cognition (Nuechterlein et al., 2008), and (3) has co-normed the MCCB (Kern et al., 2008). Training on the battery is provided via Neurcog Trials, Inc. (http://www.neurocogtrials.com). The MCCB has norms for English and Spanish versions in the United States, and co-norming and standardization of the battery are taking place in several other countries (Jedrasik-Styla et al., 2012; Mohn et al., 2012; Rapisarda et al., 2013; Rodriguez-Jimenez et al., 2011). In addition, a number of studies have now reported cognitive domain profiles based on the MCCB in adult patients with schizophrenia (August et al., 2011; Freedman et al., 2008; Javitt et al., 2012; Keefe et al., 2011; Kern et al., 2011; Marx et al., 2009; Pietrzak et al., 2009; Rajji et al., 2013; Shamsi et al., 2011; Silverstein et al., 2010), early-onset schizophrenia-spectrum disorders (Holmen et al., 2009), non-ill siblings (Nam et al., 2009), adolescents with psychotic symptoms (Kelleher et al., 2012), and youth at clinical high-risk for psychosis (De Herdt et al., 2013).

In an independent effort, the NIMH sponsored the development of the Computerized Multiphasic Interactive Neurocognitive System (CMINDS; www.neurocomp.com). The CMINDS includes computerized neuropsychological tasks that are structurally- and functionally similar to standard paper-and-pencil neuropsychological tasks (O'Halloran et al., 2008) and allows for immediate electronic raw data capture and automated scoring of test results. Among the tasks available in the CMINDS are tests similar to those of the MCCB, though they differ in administration, data capture, and scoring (for review see O'Halloran et al. (2008) and Table 1S). Some tasks also differ with regard to certain task components (Kern et al., 2009; O'Halloran et al., 2008). Unfortunately, and likely in part due to ongoing development of computerized neuropsychological batteries during the development of the MCCB, few computerized tasks, with exception of the continuous performance task, were incorporated into the MCCB. Though it could be argued that electronic data capture, which eliminates the need for manual scoring and dual data entry, has at least some efficiency advantages over paper-and-pencil neuropsychological tasks. With increases in sample sizes in all areas of psychiatric research (Ripke et al., 2011; Thompson et al., 2014), efficient data capture becomes increasingly important. In addition to the CMINDS, there are the IntegNeuro computerized cognitive assessment battery which also includes some neuropsychological test similar to standard tests (Silverstein et al., 2010) as well as several more cognitive neuroscience oriented computerized test batteries (e.g., CogState (Lim et al., 2013; Pietrzak et al., 2009), STAN/JANET (Cherkil et al., 2012; Glahn et al., 2010), CDR (Wesnes et al., 2002), PENN CNP (Gur et al., 2001a; Gur et al., 2001b; Gur et al., 2012; Gur et al., 2010) and CANTAB (Fray et al., 1996; Levaux et al., 2007), all of which are employed in numerous research studies.

In this study, we report on the CMINDS cognitive domain profile of adult patients with schizophrenia ($n=175$) compared to demographically similar healthy volunteers ($n=169$) recruited into the Function Biomedical Informatics Research Network (FBIRN) Phase 3 study. The cognitive domain scores were derived from computerized tasks that are similar to those of the paper-and-pencil MCCB. We also tested for the group and sex by domain interactions on performance. Keeping in mind that some proportion of the variance in each of the domain score distributions, for patients, is affected by a schizophrenia-related generalized cognitive impairment (e.g., poor attention) as well as factors such as poor motivation, based on the first cognitive impairment profile reported on the MCCB (Kern et al., 2011), we hypothesized the following ranking of deficits across the domains, from worst to best: Speed of Processing, Working Memory, Verbal Learning, Attention/Vigilance, Visual Learning, Reasoning/Problem Solving. Based on sex differences reported on the MCCB (Kern et al., 2008), we hypothesized a male advantage on working memory and problem solving and female advantage on verbal learning. Also, given recent evidence for confounding effects of smoking status on structural brain abnormalities (Schneider et al., 2014) as well as cognitive deficits (Hagger-Johnson et al., 2013) and the unresolved issues with regard to medication effects on cognition, we examined the effects of smoking and antipsychotic medication dosing on cognitive performance. Finally, we examined the clinical correlates of global cognitive dysfunction.

2. Methods

2.1. Participants

One-hundred-and-seventy-five patients with schizophrenia (mean age $\pm$ SD $=39.1 \pm 11.5$, 132 males) and 169 healthy volunteers (mean age $\pm$ SD $=37.6 \pm 11.3$, 122 males) with similar mean age, sex handedness, and race distributions, from 7 sites, participated in the study (see Table 1). Patient inclusion criteria were schizophrenia diagnosis based on the Structured Clinical Interview for DSM-IV-TR Axis I Disorders (First et al., 2002b). All patients were clinically stable outpatients whose antipsychotic medications and doses had not changed within the last two months. Current antipsychotic medication data were available for 159 of the 166 patients (antipsychotics: 132 atypical, 18 typical, and 9 both). Chlorpromazine equivalents (mean $\pm$ SD $=380 \pm 392$) could be computed for 143 patients (www.scottwilliamwoods.com/files/Equivtext.doc). Schizophrenia patients and healthy volunteers with a history of major medical illness, drug dependence in the last 5 years (except for nicotine), current substance abuse disorder, or MRI contraindications, were excluded. Patients with significant tardive dyskinesia and healthy volunteers with a current or past history of major neurological or psychiatric illness (First et al., 2002a) or with a first-degree relative with an Axis-I psychotic disorder diagnosis were also excluded. Patient's clinical assessments included the Positive and Negative Syndrome Scale (Kay et al., 1989), the Scale for the Assessment of Positive Symptoms (Andreasen, 1984), and the Scale for the Assessment of Negative Symptoms (Andreasen, 1983). Socioeconomic status (Hollingstead,