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.

Keywords

psychosis; neuropsychology; MATRICS; MCCB; speed of processing; memory; sex

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 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±SD=39.1±11.5, 132 males) and 169 healthy volunteers (mean age±SD=37.6±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±SD=380±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, 1975), handedness (Oldfield, 1971), basic demographics, smoking history, and premorbid IQ (Uttl, 2002) were also assessed for all subjects. The sample includes 128 paranoid, 6 disorganized, 29 undifferentiated, and 12 residual patients. Prior to data collection, experienced clinicians were jointly trained on the clinical assessment rating scales with patient interviews. The raters' assessments were compared with expert ratings. Additional training was provided when raters deviated by more than one point for each item from the expert ratings.

Written informed consent, including permission to share de-identified data between the centers and with the wider research community, approved by the University of California Irvine, Los Angeles, and San Francisco, Duke University, University of North Carolina, New Mexico, Iowa, and Minnesota Institutional Review Boards, was obtained from all study participants.

2.2 CMINDS neuropsychological test battery

The Computerized Multiphasic Interactive Neurocognitive DualDisplay System (CMINDS) (http://www.neurocomp.com/Solutions/Cminds/Default.aspx?page=Page3) includes structurally- and functionally similar, computerized administration versions of standard administration version tests selected by the NIMH-sponsored CATIE (Clinical Antipsychotic Trials of Intervention Effectiveness) and MATRICS® (Measurement and Treatment Research to Improve Cognition in Schizophrenia) consortia. These computerized tests have shown high levels of agreement with the standard tests as well as high levels of test-retest reliability (O'Halloran et al., 2008). The CMINDS battery was administered in individual testing rooms by personnel trained by neurocomp and took less than 1 hour and 30 minutes to complete.

The CMINDS test battery employed in the FBIRN Phase 3 study included the following *computerized tests* (standard equivalent, Publisher): *Finger Tapping* (Finger Tapping Test, Reitan Neuropsychological Laboratory), the *Stroop Test* (Stroop Color and Word Test, Psychological Assessment Resources, Inc), the *North American Adult Reading Test* (North American Adult Reading Test, Public Domain), the *Symbol Digit Association Test* (Symbol Digit Modalities Test, Western Psychological Services), *Trails A and B*, (Trail Making Test Parts A and B, Reitan Neuropsychological Laboratory), the *Semantic Verbal Learning Test* (Hopkins Verbal Learning Test – Revised™, Psychological Assessment Resources, Inc.), the *Visual Spatial Sequencing Test* (WMS®-III Spatial Span, Harcourt Assessment, Inc.), the *Letter Number Test* (WAIS®-III Letter Number Sequencing, Harcourt Assessment, Inc.), the *Maze Solving Test* (WISC®-III Mazes, Harcourt Assessment, Inc.), *Facial Emotion Discrimination* (Facial Emotion Discrimination, Public Domain), *Letter Fluency Test* (Letter Fluency, Public Domain), *Category Fluency Test* (Category Fluency, Public Domain), the

Visual Figure Learning Test (Brief Visuospatial Memory Test – Revised, Psychological Assessment Resources, Inc.), the *Continuous Performance Test – Repeated Pairs* (Continuous Performance Test – Identical Pairs, Biobehavioral Technologies, Inc.), and *the Card Sort Test [64 trials]* (Wisconsin Card Sort Test™, Psychological Assessment Resources, Inc.). For detailed CMINDS task descriptions see Supplement 1. For detailed descriptions of standard neuropsychological tasks see reference (Lezak, 1995). At each site, the test battery was administered by staff trained by CMINDS personnel. Prior to test administration each subject performed the CMINDS *Perception Response Evaluation Test* to determine the subject's capability of perceiving and responding to auditory and visual stimuli and prompts.

The CMINDS-based cognitive domains, based on comparable tests to those assessed by the MCCB, were as follows: (1) *Speed of Processing*. This domain score was based on the mean of (a) the log-transformed, negated (worse performance is lower) elapsed time (in seconds) during *Trails A*, (b) the number of correct in set responses in 60 seconds on trial 1 of the *Category Fluency Test – Animals*, and (c) the number of correct responses during the *Symbol Digit Association Test* z-scores; (2) *Attention/Vigilance*. This domain score was based on the d-prime across blocks A-C of the *Continuous Performance Test* z-scores; (3) *Working Memory.* This domain score was based on the mean of (a) the sum of the number of correct on the *Visual Spatial Sequencing Test* – Forward and Backward condition, and (b) the total correct on the *Letter Number Span* z-scores; (4) *Verbal Learning.* This domain score was based on the total number of correctly recalled target words for all three trials on the *Semantic Verbal Learning Test* z-scores; (5) *Visual Learning.* This domain score was based on the square-transformed total of the *Visual Figure Learning Test* z-scores, and (6) *Reasoning/Problem Solving.* This domain score was based on the square-transformed *Maze Solving Test* total score z-scores. Finally, CMINDS Composite Score was created based on the average across all 6 cognitive domains.

Examination of raw score distributions indicated that the Trails A variable (elapsed time) was notably positively skewed, while Maze Solving and Visual Figure Learning test variables were negatively skewed. The distributions for the positive and negatively skewed variables were transformed using *log* and *square* transformations, respectively. Subsequently, all tests scores were normalized to the control mean and SD *[normalized (z) score = (raw score – control mean raw score) ÷ control standard deviation].* Domain scores that consisted of multiple test scores (e.g, speed of processing, working memory, and the CMINDS composite score (mean of all 6 normalized domain scores) were normalized to the control mean and SD a second time to account for the averaging-associated changes in means and standard deviations (see Table 2 for absolute test score means as well as domain z-scores and their standard deviations).

2.3 Statistical analyses

The group comparison of the CMINDS composite score was performed using a mixed effects model (Proc Mixed, SAS/STAT® version 9.2, SAS Institute, Inc., Cary, NC, USA), predicting the normalized composite scores with group (schizophrenia, healthy volunteer), sex, age, and site. Group comparisons of the domain scores were performed using a mixed

effects model with repeated measures (MMRM). Normalized domain scores were predicted with group, domain (Speed of Processing, Attention/Vigilance, Working Memory, Verbal Learning, Visual Learning, Reasoning/Problem Solving), and the group × domain interaction. Domain was modeled as a within-subject repeated measures factor and within-subject correlations were modeled with an unstructured covariance matrix. Age, sex, and site were included as fixed effects covariates. Based on testing for group × sex, sex × domain, and group × age interactions, the sex × domain interaction was added to the model.

The significant group × domain and sex × domain interactions were followed up with 15 contrasts comparing the magnitude of the patient versus control (or female versus male) differences between each of the domains. We used the Benjamini and Hochberg (1995) (Benjamini and Hochberg, 1995) False Discovery Rate procedure (FDR<0.05) to control for Type I errors. Briefly, the pairwise comparisons were sorted (ranked) from smallest to largest pvalue and compared with the critical p-value at each rank *i*, defined as *P(i) = (i ÷ 15) · 0.05*. For all consecutive p-values for rank 1 to i, where the tests p-value < *P(i)* the null-hypothesis was rejected. In addition to the z-score profile, we also rank ordered the cognitive domain profile based on Cohen's *d* effect size estimates. To place our findings in the context of those by others, we compared our findings to those from the most recent, and largest meta-analysis study of neuropsychological task performance (Schaefer et al., 2013) as well as published neuropsychological profiles based on the MCCB (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).

Possible confounding influences of smoking status on cognitive performance deficits (Hagger-Johnson et al., 2013) were assessed by including dummy-coded smoking status (current smoker, ex-smoker, never-smoker), current pack-year, or lifetime pack-year as covariates, respectively. We also examined the relationship between domain scores and antipsychotic medication dose (chlorpromazine equivalents). Estimate statements, which produce t-statistics, were used to determine the directionality of the relationships between continuous variables (e.g., age, medication dose) and CMINDS composite and domain scores. Finally, we examine the relationships between the CMINDS composite score and several clinical variables (age at onset, duration of illness, positive and negative symptoms). A detailed analysis of individual domain scores and clinical variables is outside the scope of this study and findings will be reported on in a separate manuscript.

3. Results

3.1 CMINDS composite score

Patients (marginal mean±SE=−1.62±0.10) had significantly lower CMINDS composite scores than controls (marginal mean±SE=0.08±0.10; $t_{333}=-12.62$, $p<0.0001$) and the CMINDS composite score showed a significant negative association with age ($t_{333}=-6.66$, $p<0.0001$).

3.2 CMINDS domain profile

The MMRM analysis showed significant effects of diagnosis [$F(1,330)=201.10$, $p<0.0001$], age [$F(1,332)=68.46$, $p<0.0001$], domain [$F(5,339)=2.42$, $p<0.04$], and diagnosis × domain [$F(5,339)=4.51$, $p=0.0005$] and sex × domain interactions [$F(5,339)=3.26$, $p<0.007$], but no significant effects of site, sex, or the group × sex interaction on standardized neuropsychological domain scores.

Comparisons of group (patient vs. control) contrasts between the six cognitive domains (FDR-corrected) showed that patients were significantly more impaired than controls on the Attention/Vigilance ($t_{338}=-4.26$, $p<0.0001$), Speed of Processing ($t_{340}=-3.63$, $p=0.003$), Working Memory ($t_{339}=-3.24$, $p<0.0013$), and Verbal Learning domains ($t_{339}=-3.07$, $p=0.0023$) relative to the Reasoning/Problem Solving domain, and the Attention/Vigilance domain relative to the Visual Learning domain ($t_{338}=-2.8$, $p<0.0054$; see cognitive domain profile in Figure 1).

Comparisons of sex (female vs. male) contrasts between the six cognitive domains (FDR-corrected) showed that women were significantly better than men on the Attention/Vigilance ($t_{341}=3.22$, $p=0.0014$), Verbal Learning ($t_{339}=3.06$, $p<0.0024$), and Visual Learning ($t_{339}=2.94$, $p<0.0035$) domains relative to Reasoning/Problem Solving domain on which men excelled compared to women ($t_{338}=2.11$, p=0.04; see Figure 2).

3.3 Ranking of cognitive domain deficits based on their effect sizes

Based on Cohen's d effect sizes, the rank ordering of cognitive domain deficits for patients with schizophrenia compared to healthy controls 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 ($d=-0.67$). Patients were significantly more impaired than controls on the Attention/Vigilance, Speed of Processing, Working Memory, and Verbal Learning domains relative to the Reasoning/Problem Solving domain, and the Attention/Vigilance domain relative to the Visual Learning domain (see section 3.2 and Figure 1)."

3.4 Smoking and medication

There were no significant effects of smoking status, current or lifetime pack-year on the CMINDS composite score or on any of the individual cognitive domain scores. Among the cognitive domain scores (including the CMINDS composite score), only Reasoning/Problem Solving was significantly negatively associated with chlorpromazine dose equivalents ($t_{143}=-0.21$, $p=0.01$, uncorrected).

3.5 Clinical correlates

CMINDS composite scores showed significant negative correlations with PANSS Negative ($r=-0.23$, p<0.003), PANSS Positive ($r=-0.23$, $p<0.003$), PANSS Disorganized (item P2; $r=-0.25$, $p<0.001$), and PANSS General ($r=-0.23$, $p<0.003$) symptom severity ratings as well as duration of illness ($r=-0.30$, $p<0.0001$) but not age at onset ($r=-0.15$, $p>0.05$). The symptom correlations remained significant even after partial correlations, controlling for duration of illness, age, or age at onset, were computed. The correlation between the

CMINDS composite score and duration of illness was not significant after co-varying for the effect of age (partial r=0.06, p=0.42).

4. Discussion

This is the first study to report the CMINDS schizophrenia cognitive domain profile. The ranking of CMINDS cognitive domain deficits in patients with schizophrenia based on effect sizes 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). The cognitive domain profile based on z-scores was largely similar with the exception that the z-score for Attention/Vigilance was non-significantly lower than that of Speed of Processing. Decomposition of the significant group by domain interaction showed that patients were significantly more impaired than controls on the Attention/Vigilance, Speed of Processing, Working Memory, and Verbal Learning domains relative to the Reasoning/Problem Solving domain, and the Attention/Vigilance domain relative to the Visual Learning domain. Decomposition of the significant group by sex interaction, showed that women were significantly better than men on the Attention/Vigilance, Verbal Learning, and Visual Learning, domains relative to Reasoning/Problem Solving domain, and vice versa. Patient's cognitive deficits were not significantly associated with smoking status, or current/lifetime pack years. Among the cognitive domains, only reasoning/problem solving showed a significant negative association with medication dose in chlorpromazine equivalents. More severe cognitive impairment was associated with higher symptom severity.

The finding of the largest deficit in speed of processing and the smallest in reasoning/problem solving in patients with schizophrenia, compared to healthy volunteers, is consistent with findings from meta-analyses (Dickinson et al., 2007; Schaefer et al., 2013) as well as many, though not all (Nam et al., 2009; Shamsi et al., 2011), studies that used the MCCB (Freedman et al., 2008; Javitt et al., 2012; Keefe et al., 2011; Kern et al., 2011; Silverstein et al., 2010). Domain profiles are traditionally based on z- or T-scores, thought it could be argued that domain profiles based on effect sizes rather than z-scores are more appropriate give that effect sizes also take into account variance in the patient sample, while z- and T-score profiles do not. The effect size for speed of processing based on the CMINDS is smaller than that observed in the MCCB battery, which is most likely due to task differences in the Digit Symbol Coding task, which in the CMINDS does not require hand-eye coordination and graphomotor speed (Kern et al., 2009) because subjects provide their answers verbally instead of in writing (see (Bachman et al., 2010) for additional analyses about the contributions of cognitive processes to digit symbol coding task performance). Importantly, despite the considerable efforts in the formation of the MCCB as well as in the creation of the CMINDS, the group by domain interaction must be interpreted with caution given the inherent difficulties in establishing tests of comparable discriminability between groups across domains (Chapman and Chapman, 1973). Some attempts to create tasks of comparable discriminability have been put forward in the cognitive sciences (e.g. (Calev, 1984)) but to our knowledge such endeavors have not been undertaken for neuropsychological tests.

We did not find significant group by sex interaction effects on cognitive domain scores and the presence of differential sex effects on cognition in schizophrenia remains controversial (Krysta et al., 2013). We did find that women performed better than men on Attention/ Vigilance, Verbal Learning, and Visual Learning compared to Reasoning/Problem solving on which men performed better than women. Better performance among women than men on verbal learning and worse performance on reasoning problem solving are consistent with findings from the MCCB battery (Kern et al., 2008; Mohn et al., 2012; Rodriguez-Jimenez et al., 2011), though findings for attention/vigilance are mixed, with two studies showing better performance in men than women (Mohn et al., 2012; Rodriguez-Jimenez et al., 2011) and one showing no difference between the sexes (Kern et al., 2008). Small sex differences in performance on some neuropsychological tasks, including male advantage for some spatial tasks (e.g., block design) and female advantage for short term memory, verbal fluency, and verbal memory (Gur and Gur, 2002) are well-documented, though it has long been recognized that a simple spatial versus verbal domain accounting of sex differences is insufficient (Kolb and Whishaw, 1990). The neural underpinnings of sex differences in cognitive performance are being investigated using state-of-the art neuroimaging tools (Satterthwaite et al., 2014). A recent resting state functional magnetic resonance imaging study found that men showed stronger between-module connectivity while women showed stronger within-module connectivity and that subjects' pattern of connectivity, i.e., the relative strength of between- versus within-module connectivity, was associated with a more masculine or feminine cognition profile, even when examined within the sexes (Satterthwaite et al., 2014).

With regard to possible confounding effects of smoking, consistent with some (Van Haren et al., 2013) but not all structural imaging studies (Schneider et al., 2014), we found no confounding effect of smoking status, current pack-years, of lifetime pack-years on neurocognitive domain deficits. With regard to confounding effects of antipsychotic medications, we only found that medication dose (in chlorpromazine equivalents) predicted worse reasoning/problem solving among patients. This effect did not survive a multiple comparison corrected threshold and must therefore be treated with caution until replicated by other studies. We found significant correlations between the CMINDS composite score and negative, positive, and general symptom severity. These findings suggest that general cognitive impairment as measured by the CMINDS composite score is associated with severity of illness. The cognitive domains contributing to these significant correlations require detailed further analyses that are outside the scope of the current manuscript. While we observed a significant correlation between the CMINDS composite score and duration of illness, this correlation did not remain significant after co-varying for age. Given that we also did not observe a significant group by age interaction effect on cognitive performance, we cannot conclude that cognitive performance among patients decreases with duration of illness or is differentially influenced by age in patients with schizophrenia compared with controls.

Silverstein and colleagues (2010) have reported an increased interest in computerized neuropsychological batteries for use in clinical trails in their report on the comparison between the IntegNeuro computerized neuropsychological test battery and the MCCB (Silverstein et al., 2010). The main goal of the MATRICS initiative was to achieve a

standardized battery to test pro-cognitive agents and clearly the further development of computerized neurocognitive battery efforts should not get in the way of this important objective. Even so, given the higher efficiency of data collection, e.g., no need for manual scoring and dual data entry, the field as a whole may want to consider the use of computerized batteries. With the ever increasing sample sizes of studies aimed at making discoveries on disease etiology (Ripke et al., 2011; Thompson et al., 2014) and treatment (Keefe et al., 2011; Rajji et al., 2013), we believe that computerized batteries will have and important role to play in future cognitive assessments in neuropsychiatric disorders.

Strengths of the study are the large sample of 175 patients with schizophrenia and 169 demographically similar controls, and the use of a mature computerized test battery, the CMINDS, with tasks similar to those in the MCCB. Several weaknesses must also be noted. First, the study only included the CMINDS such that a direct comparison to the MCCB profile was not possible. A second weakness is that the CMINDS does not include tests directly comparable to the one used to measure the domain of social cognition in the MCCB. A third weakness is that the computerized digit symbol coding task differs from the paper and pencil task in that the former does not require hand-eye coordination/graphomotor integration –though, this alternative version could have advantages when assessing patients with reduced motor abilities, such as traumatic brain injury or stroke patients and may also allow for a better assessment of mental speed of processing abilities between conditions where one is confounded by motor slowing and the other is not. Finally, our study did not assess University of California Performance-Based Skills Assessment-2 (UPSA-2), which links cognitive performance to everyday functioning in schizophrenia and has been associated with the MCCB composite score (Keefe et al., 2011; Shi et al., 2013).

Strengths of the CMINDS include its ease of administration and electronic data capture and scoring, which make it very amenable to large-scale studies. In addition, the CMINDS tests are highly reliable (O'Halloran et al., 2008; O'Halloran et al., 2011) and its test scores are highly correlated with the comparable paper and pencil MCCB (O'Halloran et al., 2008) as well as Alzheimer's Disease Assessment Scale: Cognitive Subscale (ADASCog) test scores (O'Halloran et al. 2011). The CMINDS also includes parallel task versions with different stimuli to counter practice effects based on repeat administration, though to our knowledge no reports using these parallel version have been published. Therefore, the susceptibility of CMINDS test to training effects remains to be fully determined. Finally, the CMINDS is compliant with computerized clinical data collection standards, including 21 CFR Part 11, HIPAA, etc. (O'Halloran et al., 2008). A drawback is that, currently, the CMINDS does not yet provide English and Spanish norms, which may make it a less attractive choice for studies that do not include a comparison group. Advantages of the MCCB are (1) the availability of Spanish and English norms in the United States (US); moreover, norms are available or at various stages of development in numerous other countries including Spain, China, Russia, India, Central and South America, and Norway (Jedrasik-Styla et al., 2012; Kern et al., 2008; Mohn et al., 2012; Rapisarda et al., 2013; Rodriguez-Jimenez et al., 2011), and (2) its FDA-approval for use in testing pro-cognitive treatments. These features, currently, may make the MCCB the most attractive choice for clinical trails that do not include a control group.

In sum, we have reported on the CMINDS neuropsychological profile, which includes 6 of the 7 cognitive domains included in the MCCB. We conclude that the CMINDS schizophrenia cognitive domain profile show the largest impairment in speed of processing, followed by attention/vigilance, working memory, verbal learning, visual learning, and reasoning/problem solving and that the battery can readily be employed in the assessment of cognitive deficits in neuropsychiatric disorders such as schizophrenia and may be particularly useful for large-scale case-control studies in which efficient electronic data capture is most beneficial.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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- This study presents the first CMINDS® battery schizophrenia cognitive domain profile

- The schizophrenia profile shows the strongest effect size for speed of processing

- Women perform better than men on attention, speed of processing, and verbal learning

- Men perform better than women on reasoning

- Computerized neuropsychological batteries can be used in neuropsychiatric studies
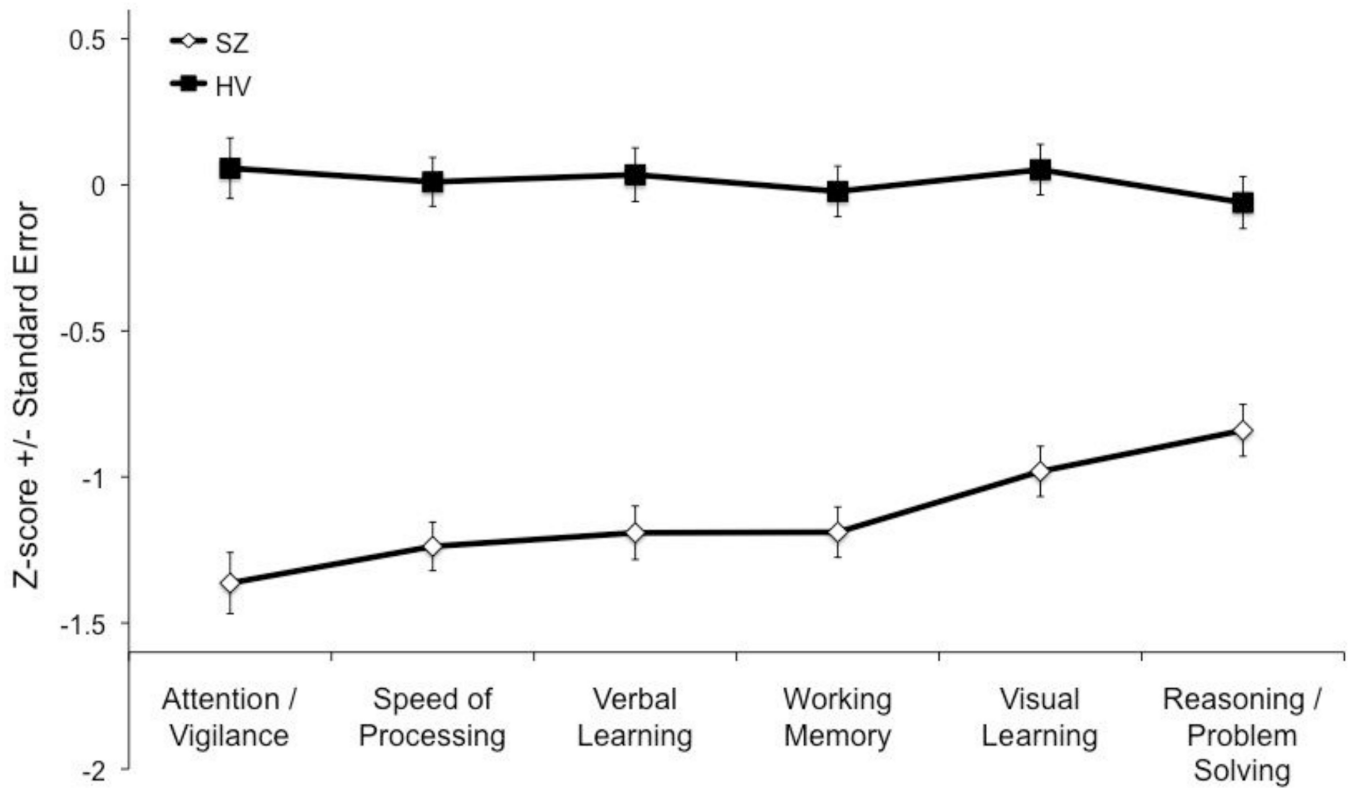
Figure 1.
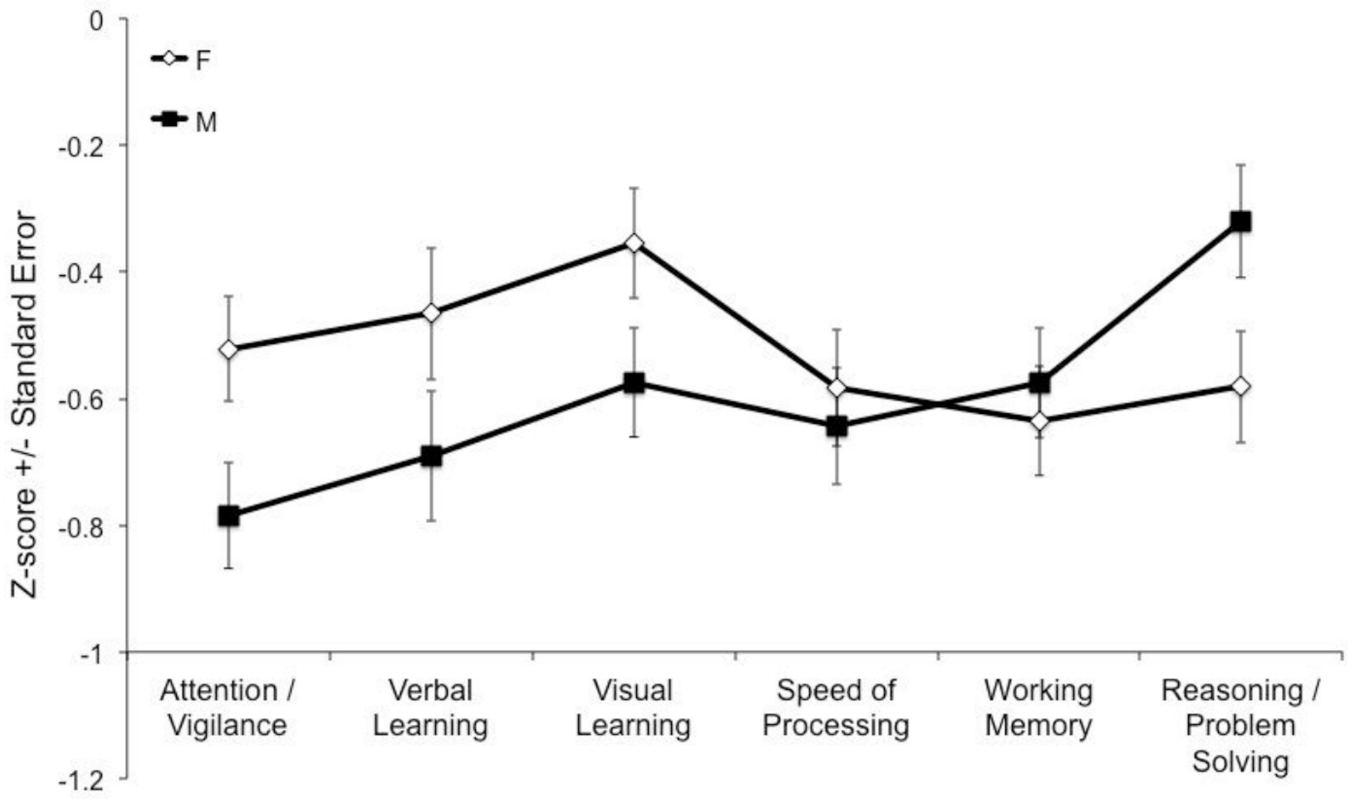CMINDS Schizophrenia Cognitive Domain Profile

Figure 2.
CMINDS Sex Differences Cognitive Domain Profile

Table 1

Sample Demographics

	Schizophrenia Patients (n=175)	Healthy Volunteers (n=169)	Statistic	p-value
Mean Age (SD)	39.1 (11.5)	37.6 (11.3)	$t_{342}=1.24$	0.22
Subject Education[b] (SD)	3.4 (1.0)	2.2 (0.9)	$t_{342}=11.46$	<0.0001
Parental Education[b] (SD)	2.3 (1.9)	2.2 (1.5)	$t_{342}=0.85$	0.40
NAART	29.6 (12.6)	39.9 (11.3)	$t_{339} = -7.99$	<0.0001
Age at Onset	21.7 (7.5)			
Duration of Illness	17.5 (11.4)			
PANSS positive	15.4 (5.0)			
PANSS negative	14.6 (5.5)			
PANSS general	28.5 (7.5)			
PANSS composite	0.8 (6.4)			
Sex (Male/Female)	132/43	122/47	$\chi^2_1=0.46$	0.49
Handedness[a] (bilateral/left/right)	3/13/159	2/8/159	FET	0.60
Race			FET	0.10
American Indian or Alaskan Native	4	3		
Asian	21	14		
Black or African American	33	18		
Native Hawaiian or Pacific Islander	3	2		
White	114	132		
Smoking Status			$X^2_2=68.5$	<0.0001
Current Smoker	81 (46%)	14 (8%)		
Ex-Smoker	32 (18%)	30 (18%)		
Never-Smoker	62 (36%)	125 (74%)		
Smoking - Current Pack-years	6.7 (13.0)	1.9 (7.2)	$t_{341}=4.2$	< 0.0001
Smoking -Lifetime Pack-years	10.7 (16.4)	2.3 (8.7)	$t_{340}=5.9$	< 0.0001

FET=Fisher's Exact Test

[a] based on Edinburgh Handedness Inventory (Oldfield, 1971)

[b] based on the Hollingstead Socioeconomic Status Scale (Hollingstead, 1975)

NAART = North American Adult Reading Test (Uttl, 2002)

PANSS = Positive and Negative Syndrome Scale (Kay et al., 1989)

Table 2

Absolute CMINDS Test Scores and Domain Z-scores by Diagnosis and Sex

Domain / Test (SD)	Schizophrenia Patients (n=175)	Healthy Volunteers (n=169)	Males (n=254)	Females (n=90)
Attention/Vigilance	−1.42 (1.43)	0 (1)	−0.81 (1.4)	−0.43 (1.4)
Continuous Performance Test (CPT)	2.3 (0.9)	3.2 (0.6)	2.7 (0.9)	3 (0.9)
Speed of Processing	−1.29 (1.09)	0 (1)	−0.69 (1.2)	−0.56 (1.23)
Trails A (TA)	36.1 (13.5)	26.3 (9.1)	31.6 (12.3)	30.4 (13.2)
Category Fluency Test (CFT)	20.1 (6.4)	24.7 (6.4)	22.2 (7)	22.7 (6.2)
Symbol Digit Association Test (SDAT)	39.3 (11.6)	53 (11.2)	45.6 (13.4)	47.2 (13.1)
Verbal Learning	−1.28 (1.2)	0 (1)	−0.73 (1.3)	−0.44 (1.27)
Semantic Verbal Learning Test (SVLT)	22.8 (5.1)	28.3 (4.3)	25.2 (5.4)	26.4 (5.4)
Working Memory	−1.21 (1.15)	0 (1)	−0.61 (1.2)	−0.61 (1.21)
Visual Spatial Sequencing Test (VSST)	13.9 (4.2)	17.2 (3.2)	15.6 (4.1)	15.2 (4)
Letter Number Test (LNT)	8.8 (2.7)	11.7 (3)	10.1 (3.3)	10.6 (3.1)
Visual Learning	−1.06 (1.14)	0 (1)	−0.61 (1.2)	−0.36 (1.12)
Visual Figure Learning Test (VFLT)	21.6 (7.7)	28.2 (5.6)	24.4 (7.7)	26 (6.9)
Reasoning/Problem Solving	−0.81 (1.24)	0 (1)	−0.36 (1.2)	−0.57 (1.15)
Maze Solving Test (MST)	22.8 (4.2)	25.3 (3.2)	24.2 (4)	23.6 (3.6)
CMINDS Composite Score	−1.66 (1.34)	0 (1)	−0.91 (1.4)	−0.66 (1.44)

Domain Z-scores are listed in **bold**. Score definitions: CPT: mean d-prime across blocks A to C; TA: elapsed time in seconds; CFT: number of in set responses in 60 seconds on trial 1; SDAT: number of correct responses; SVLT: total number of correctly recalled target words for all three trials; VSST: sum of number correct on forward and backward condition; LNT: total number correct; VFLT: total number correct; MST: total number correct.