



Contents lists available at ScienceDirect

Schizophrenia Research

journal homepage: www.elsevier.com/locate/schres

Psychometric characteristics of the MATRICS Consensus Cognitive Battery in a large pooled cohort of stable schizophrenia patients

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ARTICLE INFO

Article history:

Received 22 December 2016

Received in revised form 21 March 2017

Accepted 22 March 2017

Available online xxxx

Keywords:

Schizophrenia

Cognition

MATRICES Consensus Cognitive Battery

ABSTRACT

The MATRICS Consensus Cognitive Battery (MCCB) was developed to assess cognitive treatment effects in schizophrenia clinical trials, and is considered the FDA gold standard outcome measure for that purpose. The aim of the present study was to establish pre-treatment psychometric characteristics of the MCCB in a large pooled sample. The dataset included 2616 stable schizophrenia patients enrolled in 15 different clinical trials between 2007 and 2016 within the United States (94%) and Canada (6%). The MCCB was administered twice prior to the initiation of treatment in 1908 patients. Test-retest reliability and practice effects of the cognitive composite score, the neurocognitive composite score, which excludes the domain Social Cognition, and the subtests/domains were examined using Intra-Class Correlations (ICC) and Cohen's *d*. Simulated regression models explored which domains explained the greatest portion of variance in composite scores. Test-retest reliability was high (ICC = 0.88) for both composite scores. Practice effects were small for the cognitive ($d = 0.15$) and neurocognitive ($d = 0.17$) composites. Simulated bootstrap regression analyses revealed that 3 of the 7 domains explained 86% of the variance for both composite scores. The domains that entered most frequently in the top 3 positions of the regression models were Speed of Processing, Working Memory, and Visual Learning. Findings provide definitive psychometric characteristics and a benchmark comparison for clinical trials using the MCCB. The test-retest reliability of the MCCB composite scores is considered excellent and the learning effects are small, fulfilling two of the key criteria for outcome measures in cognition clinical trials.

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1. Introduction

Significant cognitive impairment has long been observed in schizophrenia patients. Such impairment has been well described through comparisons to both healthy individuals and patients with other psychiatric disorders (Heinrichs and Zakzanis, 1998; Keefe et al., 2005). Given the severity of these deficits and the close association between neurocognitive impairment and functional outcomes (Elvevag and Goldberg, 2000; Green et al., 2000; Heaton et al., 2001; Heinrichs and

Zakzanis, 1998; Reichenberg and Harvey, 2007) improvement of cognition has emerged as an important target in schizophrenia therapeutics.

The Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) program was initiated by the US National Institute of Mental Health (NIMH) in part to address the lack of a uniform, standardized measure of cognition to assess the effects of cognitive-enhancing drugs in schizophrenia clinical trials (Green et al., 2004; Kern et al., 2004). The MATRICS initiative selected ten individually administered tests to be included in the MATRICS Consensus Cognitive Battery (MCCB). Individual tests were selected to represent seven cognitive domains: Speed of Processing, Attention/Vigilance, Working Memory, Verbal Learning, Visual Learning, Reasoning and Problem Solving and Social Cognition. (Nuechterlein et al., 2008). The MCCB tests and domains have previously shown high test–retest reliability, good utility as repeated

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measures, strong relationships to functional outcome, changeability in response to pharmacological agents, tolerability, and practicality in both academic studies (Green et al., 2014; Kern et al., 2004) and in individual multi-site clinical trials (Keefe et al., 2011). Although these psychometric findings are encouraging, the ultimate usefulness of the MCCB in clinical trials depends on the battery's ability to demonstrate these strong psychometric characteristics within multi-site clinical trials enrolling larger and more diverse patient populations.

In the current study, we set out to establish the definitive psychometric characteristics of the MCCB by utilizing pooled patient-level data from 15 multi-site clinical trials. This database includes US and Canadian patients with stable schizophrenia who have been enrolled into treatment studies since the MCCB was made available in 2007. These data will allow researchers to compare their MCCB data with those collected from a very large sample of patients.

Additionally, since the MATRICS recommendations include the option of choosing an endpoint that comprises a subset of cognitive domains, some researchers may wish to focus on specific domains of cognition within the MCCB. The size of the current sample will allow us to establish the amount of overall variance accounted for by individual cognitive domains, and will provide an opportunity to assess the psychometric characteristics associated with individual domains and sub-tests. Our primary aims were to:

- Establish the test-retest reliability and practice effects of the MCCB cognitive and neurocognitive composite scores, domains, and subtests;
- Determine the associations between the composite scores and the individual domains and subtests;
- Determine which domains explain the greatest portion of the variance in the composite scores.

2. Methods

2.1. Study sample

A total of 2616 stable patients with a confirmed diagnosis of schizophrenia were pooled from 15 clinical trials conducted between February 2007 and July 2016. Only patients with no more than moderate severity rating on selected PANSS Items or the Brief Psychiatric Rating Scale (BPRS) were included. The pooled studies were all North American intervention studies with cognitive function in schizophrenia as one of the outcomes. The MCCB was originally developed in English for the US population but has been successfully translated to multiple foreign languages and used in many international clinical trials. Language and regional differences may have an influence on the psychometric characteristics of the MCCB and those effects would need to be tested and is outside the scope of the present study. In addition, there are language/region specific norms that should be compared to the US/English

normed data. However, that is beyond the scope of this paper and adding those comparisons would lengthen the paper considerably. Thus, only data from sites in the US and Canada are included in the analyses. Table 1 presents the studies by ClinicalTrials.gov ID number.

2.2. The MCCB

Testers were instructed to complete the MCCB in one session, which ranged from 1 to 1.5 h. The 10 subtests of the MCCB are organized into the following 7 domains:

1. Speed of Processing (SOP): Trail Making Test (TMT), BACS symbol coding, and Category Fluency.
2. Attention/Vigilance (AV): Continuous Performance Test-Identical Pairs (CPT-IP).
3. Working Memory (WM): WMS-III spatial span and Letter-Number Span (LNS).
4. Verbal Learning (VBL): Hopkins Verbal Learning Test-Revised (HVLT-R).
5. Visual Learning (VSL): Brief Visuospatial Memory Test-Revised (BVM-T-R).
6. Reasoning and Problem Solving (RPS): NAB Mazes.
7. Social Cognition (SC): MSCEIT Managing Emotions.

2.3. Data quality assurance

Training, data collection, and data quality assurance were implemented or supervised by an experienced psychologist as per the guidelines outlined in the MCCB manual (Nuechterlein et al., 2008).

2.4. MCCB composite scores

The MCCB scoring program yields T-scores that are standardized and corrected for age and sex (Nuechterlein et al., 2008). The "cognitive composite" is the standardized total of the seven domains. The "neurocognitive composite" is calculated similarly but does not include Social Cognition. In addition, a "partial average score" was calculated particularly for this paper to assess partial correlations by averaging all domains or subtests except for the one included in that specific correlation. This measure provides an estimate of the independent association of each domain or subtest with the average of the others, and thus corrects for the inflation associated with part-whole correlations.

2.5. Statistical analysis

Differences in the cognitive composite between the 15 studies were explored with an analysis of covariance (ANCOVA) at the first visit, adjusting for age and sex. ANCOVA was also used to assess the effects

Table 1
Studies included in the pooled analysis.

| ClinicalTrials.gov ID | # Subjects contributing to present analysis | Trial duration | Screening visit | Days between screening and baseline | MCCB primary outcome |
|-----------------------|---|----------------|-----------------|-------------------------------------|----------------------|
| NCT00439634 | 447 | 02/07–09/09 | No | N/A | Yes |
| NCT00505076 | 22 | 07/07–09/09 | No | N/A | Yes |
| NCT00505765 | 25 | 07/07–04/09 | No | N/A | Yes |
| NCT00641745 | 324 | 03/08–07/10 | Yes | 7–20 | Yes |
| NCT00930150 | 52 | 07/09–2/10 | No | N/A | Yes |
| NCT00968851 | 160 | 12/09–01/11 | No | N/A | No |
| NCT01077700 | 214 | 03/10–07/11 | Yes | 28–42 | Yes |
| NCT01095562 | 207 | 03/10–09/11 | Yes | 28–42 | Yes |
| NCT01192867 | 80 | 12/10–05/14 | Yes | 30–59 | No |
| NCT01192880 | 90 | 11/10–07/14 | Yes | 30–59 | No |
| NCT01192906 | 114 | 12/10–07/14 | Yes | 30–59 | No |
| NCT01568216 | 93 | 05/12–06/13 | Yes | 12–16 | No |
| NCT01655680 | 213 | 05/12–04/14 | Yes | 28–42 | Yes |
| NCT01678755 | 160 | 08/12–03/14 | Yes | 28–42 | Yes |
| NCT02281773 | 415 | 06/13–12/13 | Yes | 1–28 | No |

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