Title

Factor structure of cognitive performance and functional capacity in schizophrenia: Evidence for differences across functional capacity measures.

Authors
Harvey, Philip
Horan, William
Atkins, Alexandra
et al.

Publication Date
2020-09-01

DOI
10.1016/j.schres.2020.08.010

Peer reviewed

HHS Public Access
Author manuscript
Schizophr Res. Author manuscript; available in PMC 2021 September 11.

Published in final edited form as:
Schizophr Res. 2020 September ; 223: 297–304. doi:10.1016/j.schres.2020.08.010.

Factor Structure of Cognitive Performance and Functional Capacity in Schizophrenia: Evidence for Differences Across Functional Capacity Measures

Philip D. Harvey[1], **William P. Horan**[2,3], **Alexandra S. Atkins**[2], **Heather Stevens**[2], **Matthew Welch**[2], **Joshua Yuan**[2], **Thomas L. Patterson**[4], **Meera Narasimhan**[5], **Richard S.E. Keefe**[2,6]

[1]University of Miami Miller School of Medicine, Research Service Bruce W. Cater VA Medical Center, Miami, FL

[2]VeraSci, Durham, NC

[3]University of California, Los Angeles, CA

[4]University of California, San Diego, CA

[5]University of South Carolina, Columbia, SC

[6]Duke University, Durham, NC

Abstract

Background: Cognition and functional capacity predict functional outcomes in mental illness. Traditional approaches conceptualize cognition as comprised of domains, but many studies support a unifactorial structure. Some functional capacity measures may share a single-factor structure with cognition. In this study, we examined the factor structure of two measures of functional capacity, a conventional assessment and a newer computerized assessment, testing for a shared factor structure with cognition.

Methods: Patients with schizophrenia and healthy controls were examined with the MATRICS Consensus Cognitive Battery (MCCB), the UCSD Performance Based Skills Assessment (UPSA), and the Virtual Reality Functional Capacity Assessment Tool (VRFCAT). Models of the factor structures of the MCCB, UPSA, and VRFCAT were calculated, as were correlations between MCCB scores and individual VRFCAT objectives.

Correspondence to: Richard S.E. Keefe, PhD, Department of Psychiatry, Duke University Medical Center, DUMC Box 3270, Durham, NC 27710, United States of America. Richard.Keefe@duke.edu.

Author Contributions

Dr. Atkins, Keefe, Patterson, and Narasimhan designed the study and wrote the protocol. Drs. Harvey, Horan, Stevens, and Yuan, and Mr. Welch undertook the statistical analysis, and Dr. Harvey wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

Conflict of interest

William Horan, Alexandra Atkins, Heather Stevens, Matthew Welch, Joshua Yuan are full-time employees of VeraSci, Inc.

Results: The MCCB, VRFCAT, and UPSA all had unifactorial structures. The best fitting model of the correlations between MCCB and UPSA was a shared single factor, while the best fit for the relationship between MCCB and VRFCAT had two factors. Correlations between the MCCB domain and composite scores and the VRFCAT objectives suggested global rather than specific patterns of correlation.

Discussion: The relationship between cognitive performance and functional capacity was found to vary across functional capacity assessments. The UPSA and MCCB were not differentiated into separate factors, suggesting that the UPSA may overlap with neurocognitive performance. However, the VRFCAT appears to measure functional abilities that are separable from, yet correlated with, neurocognitive performance. It may provide a more distinctive assessment of the functional capacity construct.

INTRODUCTION

Functional capacity has been recognized for close to two decades as an important contributor to everyday disability in people with schizophrenia (SCZ) and in healthy comparisons (HC) (Patterson, et al., 2001; Harvey et al., 2007; Moore et al. 2007). Across the domains of both social and nonsocial real-world functioning, functional capacity, defined as the ability to perform critical skills that are important for completion of tasks, is correlated with successful everyday functioning (Kalin et al., 2015; Green et al., 2011). Neurocognition is an important determinant of functional capacity, with global and subdomain cognitive test scores found to correlate with performance on these measures in the moderate to large range (Leifker et al., 2011; Ventura et al., 2020). Further, the US Food and Drug Administration requires that treatment trials assessing the efficacy of pharmacological interventions or medical devices for cognitive impairment in SCZ include an assessment of the functional relevance of improvements (Buchanan et al.,2005;2010), so understanding the relationship between cognitive performance and scores on functional capacity measures is crucial. To date, there have been reports of successful treatment of deficits in functional capacity with both psychosocial (Bowie et al., 2012) and pharmacological (Javitt et al., 2012) strategies, although there have been many negative results as well. There are several issues that need to be addressed in the study of functional capacity. These include which skills are most important, how they should be assessed, and how strongly they should be related to everyday functioning on the one hand and cognition on the other. One open issue is whether different skills assessed with these measures of functional capacity should be individually related to different elements of neurocognition. For instance, should an adequate functional capacity measure contain tasks that sample each of the consensus-derived cognitive domains identified in the MATRICS initiative (e.g., working memory, verbal memory, processing speed, etc.) and show specific relations to performance on certain of these measures? Or, is it equally reasonable for a functional capacity assessment to be associated with cognition in a more global manner? When the members of the MATRICS initiative sampled existing potential co-primary functional capacity measures (Green et al., 2008; 2011), they did not make evidence of complete coverage of domains or specific relationships with cognitive performance domains a requirement for consideration, nor did they perform analyses with that goal. It could easily be argued that for a functional capacity measure to be ecologically valid, it should correlate with more than one cognitive ability domain since most functional skills enacted in daily life involve multiple cognitive processes, a common finding in studies of functional skills in individuals without impaired cognitive functioning (Czaja et al., 2010).

For a functional capacity measure to have elements that correlate differentially with specific cognitive domains, it would be important for those cognitive domains themselves to be discrete. Although the most commonly used assessment of neurocognition, the MATRICS Consensus Cognitive Battery (MCCB), samples 6 neurocognitive domains and social cognition, the recommendation from the outset by the developers of the MCCB was that the global score should be used as the primary treatment outcomes measure (Nuechterlein et al., 2008; Kern et al., 2008). The scoring program for the MCCB provides an individually normed composite score for cognitive performance. Although the MCCB was designed to measure "separable" domains (Nuechterlein et al., 2004), the term "separable" was specifically chosen so as not to suggest that the domains are independent, which they clearly are not since factor analyses of the MCCB and other test batteries in SCZ commonly yield a single-factor solution. Despite the results of some studies suggesting a more multifactorial structure (Gladsjo et al., 2004; n=206; Lo et al., 2016; n=300; McCleerey, et al., 2016: n=281), Shaefer et al. (2013) state that the finding of a global g factor for cognition is the most widely replicated finding in SCZ research. In fact, very large studies of people with SCZ often find a unifactorial structure for cognition (Keefe et al., 2006; n=1332; Harvey et al., 2016; n=4378).

There are several different strategies for assessment of functional capacity, with the most recently developed measures using technology. Because of rapidly changing technology, some widely used tests of functional capacity, such as the UCSD Performance-Based Skills Assessment (UPSA; Patterson et al., 2001; Mausbach et al., 2007), assess skills that are no longer commonly performed, particularly by younger individuals, such as calling directory assistance and writing checks. In addition, there is only a single form of the UPSA and some of the tasks are so straightforward that many people with SCZ are able to remember them at reassessment and thus manifest practice effects, which can be substantial (Keefe et al., 2016: d=.35; Harvey et al., 2010: d=.24). In contrast, the Virtual Reality Functional Capacity Assessment Task (VRFCAT; Keefe et al., 2016) is an immersive computer- or tablet-based assessment that presents subjects with series of tasks focused on preparing meals, travel and transit, money management, and shopping. Unlike most other functional capacity measures, the VRFCAT has several alternative forms and is carefully maintained to assure alignment and compatibility with newly emerging technologies. It also has socially involved and solitary activities included in its objectives (Harvey et al., 2019). Due to the variety of tasks included, the VRFCAT measures a set of functional skills that might require a variety of cognitive abilities. It is, therefore, possible that VRFCAT performance objectives would manifest differential correlations with the cognitive domains on the MCCB.

The factor structure of functional capacity measures has been studied less frequently than that of cognition, in part because these measures are not intended to comprehensively sample every important element of everyday functioning. Also, a substantial correlation between UPSA total scores and composite measures of cognition has been reported many times in the literature. These correlations may be so consistently large because the UPSA itself may not be meaningfully separable from cognitive performance. In one moderately sized study of SCZ (Harvey et al., 2013; n=195), we showed that the MCCB and UPSA combined to reflect a single latent trait that was stable at follow-up assessments conducted 6 weeks to 6 months later. In a much larger and diagnostically heterogenous sample, we identified the best fitting confirmatory factor model of cognition and the UPSA in 5,414 individuals with Bipolar Disorder I (BPI) and 3,942 SCZ patients, with a replication in 368 BPI and 436 SCZ patients. In those two samples, the best fitting factor model conceptualized the UPSA and cognition as a single ability domain, with the model fitting best when the two diagnostic groups were combined as well (Harvey et al., 2016). These results have been confirmed by the finding of substantial genomic correlations between this composite cognition-UPSA factor score (Harvey et al., 2020) and polygenic scores for both intelligence (Savage et sl., 2018) and educational attainment (Lee et al., 2018) in the general population. In this paper, the results of analyses aimed at determining whether different task objectives of the VRFCAT manifest differences in their correlations with the cognitive domains of the MCCB are reported. Using the UPSA as a comparative functional capacity measure, the factor structures of the VRFCAT and MCCB were examined. A first goal was to determine the factor structure of the VFRCAT. A multifactorial structure that would support the possibility of differential correlations of different VRFCAT task objectives with either different domains of cognition or composite scores on the MCCB, whereas a unifactorial structure would argue against this differentiation A second goal was to examine whether the factor structures of the VRFCAT and UPSA overlapped with that of the MCCB, suggesting a unifactorial factor structure of cognition and functional capacity. We hypothesized that the findings for the UPSA and MCCB would replicate previous work that indicated the UPSA was not separable from the MCCB. We further hypothesized that the VRFCAT and MCCB would define at least 2 factors and that the best fitting model would separate the MCCB and VRFCAT, because the VRFCAT measures a wider array of functionally relevant abilities, including social demands, compared to the UPSA. The final analyses were more exploratory and focused on the correlations between the MCCB, both domain and composite scores, and the VRFCAT objectives and total scores. Those analyses looked for any evidence for specific correlations between VRFCAT objectives and performance on the UPSA.

METHODS

The methods and earlier results of this study were published previously (Keefe et al., 2016; Harvey et al., 2019). As a result, the methods are presented here in an abbreviated form. Further, the analyses of the correlations of the total VRFCAT scores, cognitive test performance, and the UPSA-VIM version were previously published in detail and are not repeated in these analyses. Herein the correlations and structural relationships between domains of cognitive performance assessed by the MCCB and functional capacity as measured by the VRFCAT and UPSA were examined.

Participants

SCZ participants and healthy controls were recruited at three research sites: 1) The University of South Carolina under the supervision of Dr. Meera Narasimhan; 2) The University of Miami Miller School of Medicine under the supervision of Dr. Philip Harvey;

and 3) The University of California, San Diego School of Medicine under the supervision of Dr. Thomas Patterson.

Patients met criteria for DSM-IV TR SCZ, any subtype. All patients completed a structured diagnostic interview, administered by a trained interviewer. Patients with Positive and Negative Syndrome Scale (PANSS, Kay, et al., 1987) symptom severity scores greater than 5 (“moderately severe”) on either item P1 or P3 (delusions or hallucinatory behavior) were excluded from the study, in line with the standards for cognitive enhancement clinical trials from the MATRICS initiative (Buchanan et al, 2005; Buchanan et al, 2010). Patients were also screened for their ability to engage in testing. Those who were uncooperative, suffered from extreme cognitive impairment, had another DSM-IV diagnosis that would exclude the diagnosis of SCZ, or had severely limited eyesight were excluded. Participants who participated in studies of cognition with any of the same measures within the last 12 months were not included.

HC were excluded for a lifetime history of a psychotic disorder, bipolar disorder, or major depression. Other exclusionary criteria for both samples included inability to provide personal informed consent, history of brain trauma, documented neurologic disorder, medical conditions interfering with daily functioning, and current or recent substance abuse. Approval from the Institutional Review Board (IRB) was secured at each site and at the Sponsor site and all patients and healthy controls signed an IRB approved consent form.

There were 158 schizophrenia patients and 165 healthy controls. Of these participants, 47% of the healthy controls were female and 44% of the schizophrenia patients were female. The mean age of the schizophrenia patients was 43.6 and 42.6 for the healthy controls.

VRFCAT Description.—The VRFCAT measures four different functional abilities: checking for the availability of ingredients required to complete a recipe, taking a bus, shopping in a store, and managing currency. All participants received a brief tutorial, which included sample items similar to those from the test and practice in using the mouse and computer. Note that an updated version of the VRFCAT is now administered on a tablet computer using the touchscreen. There were 12 different task objectives, presented in Table 1. For each objective the dependent variable was time to completion. For all objectives, participants who were unable to complete the objective within 300 seconds or after 6 unsuccessful attempts were given a time to completion score of 300 seconds for that objective and automatically progressed to the next objective. Six different forms of the VRFCAT were developed and tested in this study, with forms randomized across participants. In line with the results of the validation study, these forms were combined and not examined separately in this study.

MATRICS Consensus Cognitive Battery (MCCB).—The MCCB (Nuechterlein, et al., 2008) measures seven identified domains: speed of processing; attention/vigilance; working memory (verbal and nonverbal); verbal learning; visual learning; reasoning and problem solving; and social cognition. The MCCB scoring program yields seven domain scores and a composite score, which are standardized to the same T-score measurement scale with a mean of 50 and an SD of 10 (Kern et al, 2008). Herein we excluded social cognition, examined the six individual domain scores, and created a "neurocognitive" composite score from the six domains. Administration of the MCCB requires about 75–90 minutes. The subtests were administered in the standard order.

UCSD Performance-Based Skills Assessment Validation of Intermediate Measures Version (UPSA-VIM).—We used the same version of the UPSA that was used in the MATRICS-CT Validation of Intermediate Measures study (UPSA-VIM; Green et al., 2011). The UPSA-VIM was designed to assess the ability to perform everyday tasks needed for independent community functioning. The UPSA-VIM evaluates five areas: household chores, communication, finance, transportation, and organization/planning. Raw scores from each subtest are transformed to yield comparable scores (ranging from 0 to 20) for each and a summary score ranging from 0 to 100. Higher scores reflect better performance.

Data Analyses.—A principal components analysis (PCA) followed by rotated exploratory factor analysis (EFA) strategy was used examine the factor structure of each of the three assessments (VRFCAT, MCCB, UPSA-VIM) and determine if each appeared to be unifactorial or to have a more complex factor structure. For each assessment, single factor and multifactorial solutions were computed. After determining the factor structures of the three assessments independently, two additional solutions were computed to test whether each functional capacity measure (VRFCAT and UPSA-VIM) and the MCCB constituted a single unidimensional latent trait. Analyses were conducted separately within the SCZ and HC groups, as well as in the combined sample. In a quantitative analysis, calculated goodness of fit analyses for one-factor and two-factor models in the overall sample and in the two samples separately using maximum likelihood methods were calculated. As a two-factor model hypothetically separating the two tasks is completely nested within a unifactorial model, chi-square subtraction procedures were used to examine the improvement in fit of the two-factor model compared to the unifactorial model (Raykov and Marcolides, 2011). These Chi-square values are "smaller is better" so that a Chi-square of 0 would reflect a perfect model fit and larger values reflect poorer fitting models.

In order to determine if there were any specific relationships between individual VRFCAT objectives and elements of the MCCB, Pearson Product Moment correlations between each of the 12 VRFCAT objectives and the total score were computed, as well as with the 6 MCCB domains and the neurocognitive composite score. These correlations were computed in the HC and SCZ samples separately. There were only 7 cases with missing data (out of 330), all on the VRFCAT and these participants were excluded as they were in the initial validation study paper resulting in the sample of 323 participants reported on herein.

Results

Performance on the MCCB domains, the UPSA-VIM subtests, and VRFCAT objectives are presented in Table 1.

Factor analyses

Individual measures: Unrotated PCAs suggested that each of the three assessments, VRFCAT, MCCB, and UPSA-VIM, had a unifactorial, single component structure in both the HC and SCZ samples. As can be seen in Table 2 the loadings for each of the items on the Principal component were quite similar in HC and SCZ samples. A rotated EFA using principal axis factoring with an oblique (oblimin) rotation was used to search for additional factors, with the SCZ patients and HC combined. For all three measures, the results were the same. On the VRFCAT, there was 1 of the 12 objectives that loaded higher on factor 2 than on factor 1 (objective 8: “Selecting an aisle”). However, the second factor had an eigenvalue of 0.6 as compared to an eigenvalue of 4.0 for the first factor and accounted for 5% of the variance compared to 33% for the first factor, suggesting a single dominant factor. There were no MCCB domains or UPSA-VIM subtests where the loading of any variable was higher for factor 2 than for factor 1, reflecting a clearly unifactorial solution for each measure. The loadings from the EFA 2-factor models for the combined sample for all three measures are presented in Table 3.

Combining the measures: The same strategy, rotated EFA, was used to test for unifactoriality for the MCCB and VRFCAT, and for the MCCB and UPSA-VIM. The factor analysis was calculated twice, first setting the program to extract one factor and then to extract 2. The resulting factor loadings are presented in Table 4. For the MCCB and VRFCAT analyses, the results supported a two-factor solution. The maximum likelihood EFA with oblimin rotation found two factors, with every MCCB domain loading more highly on factor 2 than factor 1 and every VRFCAT objective loading more highly on factor 1 than on factor 2. The eigenvalue for the first principal component (VRFCAT) was 6.70 (37% variance) and the eigenvalue for the second principal component (MCCB) was 1.83 (10% variance).

For the MCCB and UPSA-VIM, the results supported a unifactorial solution. The single factor solution including the MCCB domains and UPSA subtests found an Eigenvalue=5.85 and accounted for 53% of the variance. An EFA could not identify a meaningful second factor as only one of the 11 variables had a higher loading on factor 2 than 1 and the eigenvalue for the second factor was less than 1.

For both sets of analyses, the goodness of fit statistics are presented in Table 5. For the comparison of the fit characteristics of the VRFCAT and MCCB for all three analyses, the 2-factor model was a statistically significant improvement on the single-factor model and the level of significance of the Chi-square tests for the nested comparisons was very substantial. For the UPSA and MCCB analyses, the results were essentially the opposite. The two-factor model fit more poorly, as indexed by having a significantly larger chi-square value than the one-factor model for all three group comparisons. In addition, the one-factor model had a nonsignificant Chi-square for the healthy controls, reflecting a very good fit of the unifactorial model to the data.

Specificity of Correlations between VRFCAT Objectives and MCCB Domains

Intercorrelations for the VRFCAT objectives and MCCB domains are presented in Table 6. The magnitude of the correlations between each VRFCAT objective and the MCCB domains were generally quite similar for the HC and SCZ patients. Further, with some limited exceptions, each VRFCAT objective was more strongly correlated with the MCCB composite score than any of the individual domains; no correlation between any individual VRFCAT objective and an MCCB domain was significantly larger than its correlation with the MCCB composite. Also, the correlations between total VRFCAT scores and each MCCB domain were consistently larger, for both HC and SCZ patients, than the correlations between any individual VRFCAT objective and any MCCB domain. Overall, the largest correlations were between the VRFCAT total score and the MCCB neurocognitive composite score in both the HC (r = .65) and SCZ (r = .47) groups; the correlations based on total scores are extremely similar to the correlations based on the factor scores from the VRFCAT and MCCB.

DISCUSSION

This study found that the VRFCAT, a contemporary computerized measure of functional capacity, was best described as having a single-factor structure. The VRFCAT and MCCB were empirically correlated but separable, as evidenced by the robust 2-factor solution in the combined factor analyses of these measures, which improved on the fit of a unifactorial model. In contrast, the combined factor analyses confirmed our second hypothesis, that the MCCB and the UPSA-VIM would be best described by a joint unifactorial solution, consistent with several previous studies with completely non-overlapping samples (Harvey et al., 2013; 2016). Interestingly, the unifactorial solution applied equally to HC and SCZ participants, consistent with previous studies where the factor structure of the MCCB and UPSA were found to be unifactorial in SCZ and bipolar patients (Harvey et al., 2016) and where the UPSA overlapped so strongly with cognitive performance that it was excluded from analysis (Green et al., 2012). Previous studies of the VRFCAT have confirmed its consistent correlation with both measures of cognitive performance and everyday functioning in patients with SCZ, in both first episode (Ventura et al., 2020) and older patients (Keefe et al., 2016). These findings converge to suggest that the VRFCAT may provide more distinctive measure of the functional capacity construct than the UPSA, at least in terms of overlap with cognitive performance.

Exploratory analyses provided minimal evidence for specificity of relationships between VRFCAT objectives and MCCB domains, with the largest correlations being between VRFCAT total scores and MCCB composite scores. Total time to completion on the VRFCAT was consistently more strongly correlated with each MCCB domain score than were any of the individual VRFCAT objectives. Thus, in terms of specific vs. global relationships, the data from this study indicate that the VRFCAT and MCCB are more separable from each other than the MCCB cognitive domains are from each other. Further, the VRFCAT captures a unitary domain of functional capacity that is separable and distinct from the unifactorial cognitive domain captured by the MCCB, and appears to be optimally measured using a global score.

The separate factors identified in the current study for cognition and functional capacity assessed by the VRFCAT could be driven in part by its use of computerized technology compared to the UPSA, which, like 9 of 10 tests of the MCCB, uses pencil-and-paper testing. If delivery method was accounting for the variance in scores, however, then it would be expected that attention and vigilance, measured in the MCCB with a single computerized cognitive test, would be most strongly correlated with VRFCAT scores. However, scores on this domain were less strongly correlated with the VRFCAT than several other MCCB domains measured with paper and pencil. Similarly, as the main dependent variable in the VRFCAT is based on speed, speed of processing on the MCCB might be expected to have a specific relationship with VRFCAT performance or to have a cross-over loading with the VRFCAT factor. The loading is nonzero, but it is in the middle of the range of loadings for the MCCB on the VRFCAT factor.

It could be argued, however, that the VRFCAT is less redundant with tests of cognitive performance tests while still predicting some elements of real-world functional outcome that are not predicted as well by the MCCB. For instance, functional outcomes in the social domain have consistently been shown to be predicted by social competence (a measure of social functional capacity), social cognition, and negative symptoms (Kalin et al., 2015), with reduced correlations with neurocognition such as assessed by the MCCB. Negative symptoms have also been found to be strongly correlated with social outcomes in large studies (Galderisi et al., 2014; Strassnig et al., 2015), with cognitive performance and functional capacity measured by the UPSA not adding to the prediction of social outcomes in those two studies.

In contrast, the VRFCAT has been shown to be sensitive to some elements of impaired social functioning. For example, Ventura et al. reported that in early course patients VRFCAT performance predicted both social and role functioning deficits. Further, the shared variance between the VRFCAT and social functioning in that study was 22%, while the MCCB and social functioning shared 8%. Previously, patients who manifested the negative symptom of reduced emotional experience were shown to perform more poorly on VRFCAT objectives with implied or required social interactions (i.e., objectives performed away from home; Harvey et al., 2019). These emotional experience symptoms did not correlate with performance on objectives performed alone at home. Patients with poorer performance on socially relevant objectives were also found to spend significantly more time at home than patients with better performance. Thus, previous findings of sensitivity to outcomes domains not strongly correlated with the MCCB as well as correlation with the negative symptoms domains that also affect social outcomes differentiate the VRFCAT from the UPSA and are potential reasons for the findings of more independence of the VRFCAT from the MCCB.

Some limitations of this study should be considered. First, patients were not selected for any particular levels of symptoms, levels of functional deficit, or stage of illness. Second, sample sizes are smaller than some previous factor analytic studies of cognition and functional capacity. Third, social cognition was not addressed in this study. Fourth, the study did not incorporate indices of participant effort while performing tasks, although there was minimal missing data. Fifth, the MCCB has normative scores that allow for age and sex adjustments and the functional capacity measures do not; previous studies have also used raw scores for the UPSA-VIM (Green et al., 2008; 2011; Harvey et al., 2010; 2019). Finally, further research will be required to determine the relative utility of paper and pencil vs. computerized assessments in general, with direct comparisons required in terms of prediction of other variables, such as functional milestones.

Overall, these results suggest that the VRFCAT is nonredundant with cognitive performance and may contribute independently to the prediction of outcomes in SCZ. The factor structure of the VRFCAT was similar across healthy and SCZ samples. These data also provide support for the use of the VRFCAT in samples without identified serious mental illness, such as aging (Atkins et al.,2015;2018) or possibly in prodromal populations in addition to first episode patients. Additional research will be needed clarify the relative predictability of different functional domains in other populations and to determine the level of overlap between cognitive performance and VRFCAT scores in different subject samples.

Acknowledgments

Role of funding source

This study was supported by Funding was provided by the National Institute of Mental Health Grant Numbers 1R43MH084240-01A2 and 2R44MH084240-02.

In the last year, Dr. Harvey has received investigator-initiated research funding support from the Department of Veteran's Affairs, the National Institute of Aging, the US department of Veterans Affairs, and the National Institute of Mental Health. He has received consulting fees or travel reimbursements from Alkermes, BioExcel, Boehringer Ingelheim, Intra-Cellular Therapies, Minerva Pharma, Otsuka America, Regeneron, Roche Pharma, and Sunovion Pharma. He receives royalties from the Brief Assessment of Cognition in Schizophrenia and the MATRICS Consensus Battery. He has a research grant from Takeda and from the Stanley Medical Research Foundation. He is chief Scientific Officer of iFunction, inc.

Dr. Keefe is the owner of VeraSci, a company that has been paid to provide various services over the past 3 years for over 100 entities, most of which are pharmaceutical companies. VeraSci is the copyright holder of the VRFCAT and the Brief Assessment of Cognition (BAC). He has served as a consultant or Ad Board member for Merck, Akili, Avanir, GE Health, GW Pharma, Karuna, SK Life Sciences, Boehringer-Ingelheim, Jazz Pharma, Acadia, Biogen.

References

Atkins AS, Stroescu I, Spagnola NB, et al. Assessment of Age-Related Differences in Functional Capacity Using the Virtual Reality Functional Capacity Assessment Tool (VRFCAT). J Prev Alzheimers Dis. 2015;2(2):121–127. doi:10.14283/jpad.2015.61 [PubMed: 26618145]

Atkins AS, Khan A, Ulshen D, et al. Assessment of Instrumental Activities of Daily Living in Older Adults with Subjective Cognitive Decline Using the Virtual Reality Functional Capacity Assessment Tool (VRFCAT). J Prev Alzheimers Dis. 2018;5(4):216–234. doi:10.14283/jpad.2018.28 [PubMed: 30298179]

Bowie CR, McGurk SR, Mausbach B, Patterson TL, Harvey PD. 2012 Combined cognitive remediation and functional skills training for schizophrenia: effects on cognition, functional competence, and real-world behavior. Am J Psychiatry;169(7):710–718. doi:10.1176/appi.ajp.2012.11091337 [PubMed: 22581070]

Buchanan RW, Davis M, Goff D, et al. 2005 A summary of the FDA-NIMH-MATRICS workshop on clinical trial design for neurocognitive drugs for schizophrenia. Schizophr Bull;31(1):5–19. doi:10.1093/schbul/sbi020; [PubMed: 15888422]

Buchanan RW, Keefe RS, Umbricht D, Green MF, Laughren T, Marder SR. 2011 The FDA-NIMH-MATRICS guidelines for clinical trial design of cognitive-enhancing drugs: what do we know 5 years later? Schizophr Bull;37(6):1209–1217. doi:10.1093/schbul/sbq038 [PubMed: 20410237]

Czaja SJ, Sharit J, Hernandez MA, Nair SN, & Loewenstein D. 2010 Variability among older adults in Internet health information-seeking performance. Gerontechnology, 9(1), 46–55. 10.4017/gt.2010.09.01.004.00

Davies G, Lam M, Harris SE, et al. 2018 Study of 300,486 individuals identifies 148 independent genetic loci influencing general cognitive function. Nat Commun;9(1):2098 Published 2018 May 29. doi:10.1038/s41467018-04362-x [PubMed: 29844566]

Galderisi SA, Rossi A, Rocca P, Bertolino A, et al.,2014 The influence of illness-related variables, personal resources and context-related factors on real-life functioning of people with schizophrenia. World Psychiatr. 13,275–287.

Gladsjo JA, McAdams LA, Palmer BW, Moore DJ, Jeste DV, Heaton RK. 2004 A six-factor model of cognition in schizophrenia and related psychotic disorders: relationships with clinical symptoms and functional capacity. Schizophr Bull4;30(4):739–754. doi:10.1093/oxfordjournals.schbul.a007127

Green MF, Hellemann G, Horan WP, Lee J, Wynn JK. 2012 From perception to functional outcome in schizophrenia: modeling the role of ability and motivation. Arch Gen Psychiatry;69(12):1216–1224. doi:10.1001/archgenpsychiatry.2012.652 [PubMed: 23026889]

Green MF, Nuechterlein KH, Kern RS, et al. 2008 Functional co-primary measures for clinical trials in schizophrenia: results from the MATRICS Psychometric and Standardization Study. Am J Psychiatry.;165(2):221–228. doi:10.1176/appi.ajp.2007.07010089 [PubMed: 18172017]

Green MF, Schooler NR, Kern RS, et al. 2011 Evaluation of functionally meaningful measures for clinical trials of cognition enhancement in schizophrenia. Am J Psychiatry;168(4):400–407. doi:10.1176/appi.ajp.2010.10030414 [PubMed: 21285142]

Harvey PD, Aslan M, Du M, et al. 2016 Factor structure of cognition and functional capacity in two studies of schizophrenia and bipolar disorder: Implications for genomic studies. Neuropsychology;30(1):28–39. doi:10.1037/neu0000245 [PubMed: 26710094]

Harvey PD, Khan A, Atkins A, Keefe RS. 2019 Virtual reality assessment of functional capacity in people with Schizophrenia: Associations with reduced emotional experience and prediction of functional outcomes. Psychiatry Res;277:58–63. doi:10.1016/j.psychres.2019.01.045 [PubMed: 30679049]

Harvey PD, Raykov T, Twamley EW, Vella L, Heaton RK, Patterson TL. 2013 Factor structure of neurocognition and functional capacity in schizophrenia: a multidimensional examination of temporal stability. J Int Neuropsychol Soc;19(6):656–663. doi:10.1017/S1355617713000179 [PubMed: 23425725]

Harvey PD, Reichenberg A, Bowie CR, Patterson TL, Heaton RK. 2010 The course of neuropsychological performance and functional capacity in older patients with schizophrenia: influences of previous history of long-term institutional stay. Biol Psychiatry;67(10):933–939. doi:10.1016/j.biopsych.2010.01.008 [PubMed: 20202624]

Harvey PD, Sun N, Bigdeli TB, et al. 2020 Genome-wide association study of cognitive performance in U.S. veterans with schizophrenia or bipolar disorder. Am J Med Genet B Neuropsychiatr Genet;183(3):181–194. doi:10.1002/ajmg.b.32775 [PubMed: 31872970]

Harvey PD, Velligan DI, Bellack AS. 2007 Performance-based measures of functional skills: usefulness in clinical treatment studies. Schizophr Bull;33(5):1138–1148. doi:10.1093/schbul/sbm040 [PubMed: 17493956]

Javitt DC, Buchanan RW, Keefe RS, et al. 2012 Effect of the neuroprotective peptide davunetide (AL-108) on cognition and functional capacity in schizophrenia. Schizophr Res;136(1–3):25–31. doi:10.1016/j.schres.2011.11.001 [PubMed: 22169248]

Kalin M, Kaplan S, Gould F, Pinkham AE, Penn DL, Harvey PD. 2015 Social cognition, social competence, negative symptoms and social outcomes: Inter-relationships in people with schizophrenia. J Psychiatr Res.;68:254–260. doi:10.1016/j.jpsychires.2015.07.008 [PubMed: 26228427]

Kay SR, Fiszbein A, Opler LA 1987 The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr. Bull 13, 261–276. [PubMed: 3616518]

Keefe RS, Bilder RM, Harvey PD, et al. 2006 Baseline neurocognitive deficits in the CATIE schizophrenia trial. Neuropsychopharmacology. 2006;31(9):2033–2046. doi:10.1038/sj.npp.1301072 [PubMed: 16641947]

Keefe RSE, Davis VG, Atkins AS, et al. 2016 Validation of a Computerized test of Functional Capacity. Schizophr Res;175(1–3):90–96. doi:10.1016/j.schres.2016.03.038 [PubMed: 27091656]

Keefe RS, Poe M, Walker TM, Kang JW, Harvey PD. 2006 The Schizophrenia Cognition Rating Scale: an interview-based assessment and its relationship to cognition, real-world functioning, and functional capacity. Am J Psychiatry;163(3):426–432. doi:10.1176/appi.ajp.163.3.426 [PubMed: 16513863]

Kern RS, Nuechterlein KH, Green MF, et al. 2008 The MATRICS Consensus Cognitive Battery, part 2: co-norming and standardization. Am J Psychiatry;165(2):214–220. doi:10.1176/appi.ajp.2007.07010043 [PubMed: 18172018]

Lee JJ, Wedow R, Okbay A, et al. 2018 Gene discovery and polygenic prediction from a genome-wide association study of educational attainment in 1.1 million individuals. Nat Genet;50(8):1112–1121. doi:10.1038/s41588-018-0147-3 [PubMed: 30038396]

Leifker FR, Patterson TL, Heaton RK, Harvey PD. 2013 Validating measures of real-world outcome: the results of the VALERO expert survey and RAND panel. Schizophr Bull;37(2):334–343. doi:10.1093/schbul/sbp044

Lo SB, Szuhany KL, Kredlow MA, Wolfe R, Mueser KT, McGurk SR. 2016 A confirmatory factor analysis of the MATRICS consensus cognitive battery in severe mental illness. Schizophr Res;175(1–3):79–84. doi:10.1016/j.schres.2016.03.013 [PubMed: 27041675]

McCleery A, Green MF, Hellemann GS, et al. 2016 Latent structure of cognition in schizophrenia: a confirmatory factor analysis of the MATRICS Consensus Cognitive Battery (MCCB). Psychol Med.;45(12):2657–2666.

McClure MM, Bowie CR, Patterson TL, et al. 2007 Correlations of functional capacity and neuropsychological performance in older patients with schizophrenia: evidence for specificity of relationships?. Schizophr Res;89(1–3):330–338. doi:10.1016/j.schres.2006.07.024 [PubMed: 16982175]

Mausbach BT, Harvey PD, Goldman SR, Jeste DV, Patterson TL. 2007 Development of a brief scale of everyday functioning in persons with serious mental illness. Schizophr Bull;33(6):1364–1372. doi:10.1093/schbul/sbm014 [PubMed: 17341468]

Moore DJ, Palmer BW, Patterson TL, Jeste DV. 2007 A review of performance-based measures of functional living skills. J Psychiatr Re;41(1–2):97–118. doi:10.1016/j.jpsychires.2005.10.008

Nuechterlein KH, Barch DM, Gold JM, Goldberg TE, Green MF, Heaton RK. 2004 Identification of separable cognitive factors in schizophrenia. Schizophr Re;72(1):29–39. doi:10.1016/j.schres.2004.09.007

Nuechterlein KH, Green MF, Kern RS, et al. 2008 The MATRICS Consensus Cognitive Battery, part 1: test selection, reliability, and validity. Am J Psychiatr;165(2):203–213. doi:10.1176/appi.ajp.2007.07010042 [PubMed: 18172019]

Patterson TL, Goldman S, McKibbin CL, Hughs T, Jeste DV. 2001 UCSD Performance-Based Skills Assessment: development of a new measure of everyday functioning for severely mentally ill adults. Schizophr Bull.;27(2):235–245. doi:10.1093/oxfordjournals.schbul.a006870 [PubMed: 11354591]

Raykov T, and Marcolides G. 2011 Introduction to Psychometric Theory. London, Taylor and Francis.

Ruse SA, Harvey PD, Davis VG, Atkins AS, Fox KH, Keefe RSE 2014 Virtual reality functional capacity assessment in schizophrenia: Preliminary data regarding feasibility and correlations with cognitive and functional capacity performance. Schizophr. Res. Cogn 1: 21–26

Schaefer J, Giangrande E, Weinberger DR, Dickinson D. 2013 The global cognitive impairment in schizophrenia: consistent over decades and around the world. Schizophr Res;150(1):42–50. doi:10.1016/j.schres.2013.07.009 [PubMed: 23911259]

Savage JE, Jansen PR, Stringer S, et al. 2018 Genome-wide association meta-analysis in 269,867 individuals identifies new genetic and functional links to intelligence. Nat Genet;50(7):912–919. doi:10.1038/s41588-0180152-6 [PubMed: 29942086]

Strassnig MT, Raykov T, O'Gorman C, et al. 2015 Determinants of Different Aspects of Everyday Outcome in Schizophrenia : The Roles of Negative Symptoms, Cognition, and Functional Capacity. Schizophr. Res 165, 76–82. [PubMed: 25868935]

Ventura J, Welikson T, Ered A, et al. 2020 Virtual reality assessment of functional capacity in the early course of schizophrenia: Associations with cognitive performance and daily functioning. Early Interv Psychiatry;14(1):106–114. doi:10.1111/eip.12831 [PubMed: 31183960]

Table 1

Performance on the VRFCAT Objectives, MCCB Domain and Neurocognitive Composite Scores, and the UPSA Subscales

	Participants with Schizophrenia (N=158)		Healthy Controls (N=165)	
VRFCAT Objectives				
Time to completion	M	SD	M	SD
1. Pick up Recipe	57.07	18.14	51.19	3.81
2. Search for Ingredients	92.45	44.57	74.22	23.45
3. Cross Off Items	178.38	65.00	123.10	60.70
4. Pick up Billfold	31.01	21.83	25.44	3.52
5. Exit the Apartment	29.16	18.04	24.14	2.77
6. Take the Correct Bus	71.90	20.36	66.99	11.35
7. Pay the Bus Fare	74.77	44.61	57.11	19.11
8. Select an Aisle	42.25	15.34	38.11	7.68
9. Shop and Check out	200.84	72.41	132.63	60.94
10. Pay for Purchases	100.60	65.05	65.19	34.53
11. Select Correct Bus Home	68.61	9.71	66.68	14.68
12. Pay the Bus Fare	118.11	72.50	74.43	44.87
Total Time	1065.16	321.46	799.15	187.37
MCCB Domains				
Expressed as T-scores	M	SD	M	SD
Speed of Processing	32.87	12.05	46.64	10.05
Working Memory	35.68	13.11	45.79	12.31
Verbal Memory	36.54	8.98	46.68	10.81
Visual Memory	33.89	12.55	44.84	11.72
Reasoning and problem Solving	40.46	10.11	46.20	10.10
Attention/Vigil ance	35.87	12.18	45.84	10.97
Composite	27.45	13.30	44.01	13.23
UPSA Subscales				
Raw Scores	M	SD	M	SD
Comprehension and Planning	12.97	4.13	16.68	2.67
Finances	16.35	3.32	18.71	1.79
Communication	11.46	3.69	14.69	3.47
Transportation	14.23	2.96	15.98	2.84
Home Maintenance	15.09	4.25	17.21	3.10
Total	70.11	12.66	83.25	9.05

Table 2

Exploratory Factor Solutions for VRFCAT, MCCB, and UPSA-VIM: Patients and Controls Separated

VRFCAT	Component Loading	
	Participants with Schizophrenia (N=158)	**Healthy Controls (N=165)**
1. Pick up Recipe	.80	.61
2. Search for Ingredients	.67	.55
3. Cross Off Items	.57	.72
4. Pick up Billfold	.70	.56
5. Exit the Apartment	.35	.53
6. Take the Correct Bus	.70	.38
7. Pay the Bus Fare	.67	.61
8. Select an Aisle	.49	.38
9. Shop and Check out	.66	.79
10. Pay for Purchases	.71	.48
11. Select Correct Bus Home	.86	.50
12. Pay the Bus Fare	.68	.66
Eigen Value	4.51	3.84
% Variance	44	32
MCCB	**Component Loading**	
Speed of Processing	.80	.84
Working Memory	.84	.83
Verbal Memory	.68	.74
Visual Memory	.73	.77
Reasoning and problem Solving	.74	.70
Attention/Vigilance	.77	.75
Eigenvalue	3.49	3.57
% Variance	58	60
	Component Loading	
UPSA-VIM		
Comprehension and Planning	.61	.65
Finances	.68	.71
Communication	.77	.78
Transportation	.70	.66
Home Maintenance	.52	.43
EigenValue	2.25	2.15
% Variance	32	33

Table 3

EFA for 2-Factor Models for VRFCAT, MCCB, and UPSA-VIM: Patients and Controls Combined

VRFCAT	Component Loading	
	Factor 1	Factor 2
1. Pick up Recipe	.58	.26
2. Search for Ingredients	.52	.00
3. Cross Off Items	.72	.12
4. Pick up Billfold	.46	.23
5. Exit the Apartment	.41	.00
6. Take the Correct Bus	.38	.37
7. Pay the Bus Fare	.39	−.32
8. Select an Aisle	.32	.37
9. Shop and Check out	.82	.00
10. Pay for Purchases	.71	−.41
11. Select Correct Bus Home	.38	.00
12. Pay the Bus Fare	.73	−.16
Eigen Value	3.91	.57
% Variance	33	5
MCCB	Component Loading	
	Factor 1	Factor 2
Speed of Processing	.86	.16
Working Memory	.85	−.03
Verbal Memory	.76	−.06
Visual Memory	.78	−.39
Reasoning and problem Solving	.73	−.25
Attention/Vigilance	.78	.60
Eigen Value	3.6	.60
% Variance	63	6
UPSA-VIM		
	Component Loading	
	Factor 1	Factor 2
Comprehension and Planning	.63	−.18
Finances	.67	.18
Communication	.77	−.13
Transportation	.57	.00
Home Maintenance	.42	.30
Eigen Value	1.92	.12
% Variance	38	2

Table 4

Factor Models for VRFCAT, MCCB, and UPSA-VIM Participant Samples Combined

Single Factor Model for VRFCAT and MCCB		
VRFCAT	Component Loading	
	Factor 1	
1.Pick up Recipe	.51	
2. Search for Ingredients	.51	
3 Cross Off Items	.68	
4. Pick up Billfold	.36	
5. Exit the Apartment	.40	
6. Take the Correct Bus	.35	
7. Pay the Bus Fare	.56	
8. Select an Aisle	.41	
9. Shop and Check out	.74	
10. Pay for Purchases	.65	
11. Select Correct Bus Home	.46	
12. Pay the Bus Fare	.71	
MCCB		
Speed of Processing	−.73	
Working Memory	−.75	
Verbal Memory	−.65	
Visual Memory	−.69	
Reasoning and problem Solving	−.57	
Attention/Vigilance	−.68	
EigenValue	6.95	
% Variance	39	
Two Factor Model for VRFCAT and MCCB		
VRFCAT	Component Loading	
	Factor 1	Factor 2
1.Pick up Recipe	.61	−.38
2. Search for Ingredients	.56	−.27
3. Cross Off Items	.67	−.55

4. Pick up Billfold	.46	−.27
5. Exit the Apartment	.38	−.23
6. Take the Correct Bus	.39	−.21
7. Pay the Bus Fare	.61	−.34
8. Select an Aisle	.40	−.24
9. Shop and Check out	.78	−.57
10. Pay for Purchases	.70	−.44
11. Select Correct Bus	.41	−.27
12. Pay the Bus Fare	.71	−.52
MCCB		
Speed of Processing	−.49	.83
Working Memory	−.53	.82
Verbal Memory	−.46	.71
Visual Memory	−.49	.73
Reasoning and problem Solving	−.35	.68
Attention/Vigilance	−.44	.75
EigenValue	6.70	1.83
% Variance	37	10
Single Factor Model for UPSA-VIM and MCCB		
	Component Loading	
UPSA-VIM	Factor 1	
Comprehension and Planning	.62	
Finances	.67	
Communication	.71	
Transportation	.59	
Home Maintenance	.47	
MCCB		
Speed of Processing	.82	
Working Memory	.83	
Verbal Memory	.73	
Visual Memory	.76	
Reasoning and problem Solving	.67	

Attention/Vigilance	.77	
EigenValue	5.85	
% Variance	53	
Two Factor Model for UPSA-VIM and MCCB		
	Component Loading	
UPSA-VIM	Factor 1	Factor 2
Comprehension and Planning	.76	.02
Finances	.62	.06
Communication	.33	.45
Transportation	.55	.05
Home Maintenance	.44	.04
MCCB		
Speed of Processing	.75	.10
Working Memory	.95	−.13
Verbal Memory	.45	.37
Visual Memory	.51	.31
Reasoning and problem Solving	.71	.05
Attention/Vigilance	.83	.06
EigenValue	5.85	.84
% Variance	53	8

See Table 5 for fit statistics.

Table 5

Goodness of Fit Statistics for One and Two Factor Models for the Three Performance Based Measures

VRFCAT and MCCB									
	2 Factor			1 Factor			Difference		
	X^2	df	p	X^2	df	p	X^2	df	p
Total Sample	484.0	118	.001	913.6	135	.001	429.6	17	.001
Schizophrenia	391.9	118	.001	614.9	135	.001	223.0	17	.001
Healthy Controls	253.5	118	.001	401.2	135	.001	147.7	17	.001
UPSA-VIM and MCCB									
	2 Factor			1 Factor			Difference		
	X^2	df	p	X^2	df	p	X^2	df	p
Total Sample	80.9	44	.001	65.1	34	.001	15.8	10	.10
Schizophrenia	119.4	44	.001	102.4	34	.001	19.0	10	.04
Healthy Controls	62.9	44	.001	42.1	34	.16	20.8	10	.021

Note. For goodness of fit, smaller is better.

Author Manuscript

Author Manuscript

Author Manuscript

Table 6

Correlation of VRFCAT Objectives and MCCB Domains

VRFCAT Objectives		MCCB Domains						
		SOP	WM	VerM	VisM	R/PS	A/VIS	Neurocognitive Composite
1. Pick up Recipe	SCZ	−.35	−.28	−.18	−.17	−.17	−.32	−.32
	HC	−.31	−.28	−.28	−.32	−.13	−.24	−.34
2. Search for Ingredients	SCZ	−.23	−.19	−.13	−.18	−.11	−.11	−.16
	HC	−.23	−.17	−.25	−.22	−.11	−.12	−.24
3. Cross Off Items	SCZ	−.31	−.37	−.28	−.23	−.32	−.23	−.39
	HC	−.28	−.41	−.35	−.35	−.31	−.36	−.50
4. Pick up Billfold	SCZ	−.25	−.08	−.11	−.15	−.05	−.14	−.26
	HC	−.22	−.29	−.30	−.25	−.17	−.19	−.30
5. Exit the Apartment	SCZ	−.17	−.19	−.07	−.21	−.10	−.08	−.21
	HC	−.23	−.16	−.20	−.26	−.15	−.08	−.24
6. Take the Correct Bus	SCZ	−.32	−.27	−.12	−.18	−.12	−.24	−.26
	HC	−.06	−.04	−.13	−.12	−.01	−.14	−.11
7. Pay the Bus Fare	SCZ	−.22	−.30	−.15	−.26	−.11	−.20	−.27
	HC	−.27	−.33	−.24	−.33	−26	−.29	−.46
8. Select an Aisle	SCZ	−.23	−.26	−.15	−.26	−11	−.20	−.26
	HC	−.10	−.13	−.10	−.12	−.21	−.00	−.14
9. Shop and Check out	SCZ	−.21	−.32	−.28	−.31	−.20	−.31	−.38
	HC	−.41	−.46	−.40	−.42	−.36	−.32	−.52
10. Pay for Purchases	SCZ	−.25	−.37	−.15	−.29	−.20	−.26	−.33
	HC	−.30	−.37	−.37	−.26	−23	−.36	−.45
11. Select Correct Bus Home	SCZ	−.35	−.33	−.14	−.23	−.18	−.22	−.36
	HC	−.23	−.26	−.14	−..22	−.10	−.28	−.23
12. Pay the Bus Fare	SCZ	−.26	−.42	−.27	−.30	−.23	−.30	−.40
	HC	−.43	−.50	−.35	−.42	−.25	−.40	−.51
Total Time	SCZ	−.37	−.46	−.28	−.37	−.29	−.34	−.47
	HC	−.51	−.56	−.49	−.50	−.38	−.47	−.65

Note. Correlations >r=.14 are significant at p<.05 for HC; r>.15 p<.05, for SCZ