Current Topics in Behavioral Neurosciences 63

Deanna M. Barch
Jared W. Young *Editors*

# Cognitive Functioning in Schizophrenia: Leveraging the RDoC Framework

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Editors

# Cognitive Functioning in Schizophrenia: Leveraging the RDoC Framework

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# Preface

## Cognition Is Vital to Living for People with Schizophrenia

Throughout the long history of conceptions of schizophrenia, dysfunctional cognition has been a hallmark feature. For example, in the late 1800s schizophrenia was first termed *dementia praecox*, meaning premature dementia. With the advent of antipsychotic therapies in the 1950s, the focus for treatment moved to the positive symptoms that characterize schizophrenia, such as hallucinations and delusions, as these were responsive to such treatments, at least in some individuals. However, antipsychotic therapies did little to address the cognitive challenge so often present for people with schizophrenia. As such, more recently (in the late 1900s), cognitive dysfunction was again identified as the pre-eminent aspect of schizophrenia that required treatment given that it most closely associated with a person's functional outcome. In other words, a patient's ability to function independently in society, their connection to their families and friends were most strongly associated with their cognitive functioning. From this evidence, researchers re-focused efforts on identifying potential treatments for the cognitive dysfunction that so frequently accompanies the disorder.

There have been many barriers faced by researchers trying to improve cognition in schizophrenia however. From the heterogeneity of cognitive dysfunction to variability in assessment tools, to rapid advancement in neuroscientific techniques, each area provides a vast array of research that requires distillation. To address potential heterogeneity and transdiagnostic qualities of cognitive dysfunction (such deficits also occur in other disorders), the National Institute of Mental Health (NIMH) began the Research Domain Criterion (RDoC) initiative. RDoC was designed as a platform by which specific domains of dysfunction could be identified irrespective of diagnosis, on the premise that the same neurobiology underlies functioning in people, thus if affected by disease it will likely be similarly affected irrespective of disease. Hence, the use of RDoC at least has the chance to reduce some of the heterogeneity limitations of research because of a greater shared

language and focus on specific domains than had been used previously. The RDoC approach has only been around for ~10 years but offers great hope for tying together such a vast array of research on cognition in schizophrenia. Ultimately, our knowledge of the cognitive deficits that occur in people with schizophrenia, their potential developmental trajectory, genetic and environmental etiology, and potential neural mechanisms have greatly advanced in the past 20 years. In this book, we brought together experts on this cognitive research and where possible, they have attempted to tie such mechanistic and treatment insights to a common language utilizing RDoC. Views from across the research spectrum are incorporated and the reader will hopefully have a greater appreciation for the progress of this research in the past two decades as well as the avenues in need of further pursuit.

Cognitive deficits have been well-documented in people at high risk of developing schizophrenia and occur in people before their first psychotic episode. Dr. Karcher covers cognitive dysfunction as a risk factor for psychosis. They provide evidence that cognitive deficits may be an intermediate risk factor linking genetic and/or neural metrics to psychosis spectrum symptoms. Although specific RDoC-related domains have rarely been tested and not yet been associated with psychosis, the greatest severity of cognitive deficits has been linked to the development of psychotic symptoms. Research on potential associative mechanisms is described, which may relate to specific domains that require further research. Identification of such mechanisms and domains would enable the development of treatments that may delay/prevent the onset of psychosis.

In a more specific focus on particular domains of information processing, Dr. Giersch and Laprévote then discuss alterations in perceptual functioning in people with schizophrenia, specifically focusing on visual perception. As with cognitive deficits, abnormalities in visual perception are seen in the prodromal phase of schizophrenia, leading to difficulties adapting to surroundings. RDoC-based aspects of perception are discussed, such as contrast sensitivity, masking, visual group, and temporal perception. Identifying which domains may predict the development of psychosis, as with other cognitive domains, could enable treatment development blocking the progression to psychosis.

When first attempting to develop such treatments for cognitive dysfunction in people with schizophrenia, issues quickly arose. For one, the Federal Drug Agency (FDA) had no mechanism by which a drug could be approved that treated cognitive dysfunction associated with schizophrenia. Thus, the NIMH funded the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) initiative. The MATRICS process brought together academia, the pharmaceutical industry, and the FDA, identifying: (1) cognitive domain targets in schizophrenia; (2) promising molecular targets to enhance these domains; and importantly (3) a process of approval for potential therapeutics to treat these domains in schizophrenia. MATRICS identified seven cognitive domains most affected in people with schizophrenia including attention/vigilance, speed of processing, reasoning and problem solving, verbal learning and memory, visual learning and memory, working memory, and social cognition. From this work, they then identified the MATRICS

consensus cognitive battery (MCCB), for which to quantify dysfunction in each domain and test whether treatments were efficacious in treating such cognitive difficulties. This work and an update on the research conducted to-date using their developed test battery were covered in the chapter by Dr. Neuchterlein and colleagues.

Interestingly, the evolution of MATRICS resulted in attempts to tie cognitive functioning more closely to neural mechanisms by utilizing another NIMH-funded initiative, the Cognitive Neuroscience Treatment Research to Improve Cognition in Schizophrenia (CNTRICS). This work recognized the need to move from paper-and-pen tests of cognition to more laboratory and cognitive neuroscience-based assessments. Hence, the leaders of this approach, Drs. Barch and Carter brought experts together and further narrowed the definition of cognitive deficits in people with schizophrenia so that they more likely reflect altered neural mechanisms. Importantly, this work also brought in animal researchers so that cross-species research engaging such mechanisms could be conducted. In their chapter, Dr. Barch and colleagues describe the evolution of CNTRICS and its testing platform, providing links where appropriate to domains identified by RDoC. Hence, future research will continue to be applicable when generated from this platform.

Evidence for research conducted on specific examples of RDoC-cited domains is then provided, with Dr. Luck and colleagues describing that while attention is a core area of cognitive dysfunction in people with schizophrenia, attention is complex and multifaceted, separated out by the RDoC initiative. Within this chapter, they discuss how people with schizophrenia have: (1) a reduction in global alertness, (2) deficits in visual attention only when the stimuli activate the magnocellular processing pathway, and (3) hyperfocused attention to goal-irrelevant information. By providing such detailed information on the attentional deficits in people with schizophrenia, targeted therapeutics can be generated.

The work on attention dovetails well with assessment of working memory in people with schizophrenia, as described by Drs. Gold and Luck. Using the RDoC initiative representation, they describe how working memory representations are held in a 'privileged' state that are easily retrieved and relatively immune to distracting events. Furthermore, given that working memory is fundamental to reasoning, decision-making, cognitive control, etc., detailing changes in patients with schizophrenia remains vital. Mechanisms underlying working memory deficits in patients with schizophrenia, and links to other cognitive domains, are described.

Working memory differs from other aspects of memory such as episodic memory, with research in this domain covered by Dr. Raucher-Chene and colleagues. Episodic memory refers to the associations or binding among items or elements presented together, with cognitive neuroscience relevant to RDoC domains identifying mechanisms related to such specific processes. Furthermore, fMRI biomarkers of episodic memory deficits in people with schizophrenia are identified and discussed, all distinct from those of working memory.

Importantly, these early chapters provide evidence for circuitry likely disrupted in people with schizophrenia, potentially related to specific cognitive domains. Thus, at both the neuronal and local levels, treatments can be targeted at these regions. Drs. I-

Wei Shu and Eric Granholm provide an overview on how targeting frontal gamma – affected in people with schizophrenia measurable during cognitive testing – with neurofeedback offers opportunities to selectively target structures affected by the disease process. This top-down process of identifying cognitive deficits and directly targeting circuits affected has provided compelling data for efficacy, but the work requires further exploration. Regarding pharmacological treatments, Dr. Horan and colleagues then provide an update on such studies for cognitive dysfunction in people with schizophrenia. Although no treatments have passed Phase III trials to-date, there is a glutamatergic-based drug that is currently undergoing testing that shows some promise. Importantly, positive findings have been reported and the authors highlight this work and how transdiagnostic approaches may aid in more targeted therapeutics via the identification of homogeneous subgroups. Hence, future opportunities continue to arise for the targeted therapeutic development of cognitive impairment associated with schizophrenia.

A great deal of additional research has been conducted from a bottom-up perspective also, trying to discover mechanisms affected by the disease process and how they affect cognitive dysfunction that occurs in people with schizophrenia. For example, Dr. Tiffany Greenwood describes the evidence for the multiple genetic abnormalities that occur in people with schizophrenia, describing genetic networks that largely underpin synaptic pruning and neural development at a very young age. Dr. Lipner et al describe how environmental factors can play a role in driving neural changes that are associated with cognitive deficits in people with schizophrenia. Each of these mechanisms may work alone and/or synergistically to result in the cognitive deficits in people with schizophrenia, but understanding their mechanisms offers targeting opportunities for therapeutic development.

The information on potential causes underlying schizophrenia, alterations in neural mechanisms, and information on positive and negative therapeutic effects are all vital for preclinical researchers, such as the work of Dr. Kentner and colleagues. This group describes early-life developmental manipulations that can be conducted in rodents and tools to assess cognitive outcomes based on RDoC-relevant tasks. The validity of these disease-relevant manipulations, the impact of potential treatments, and their utility for treatment-development research are all discussed. Furthermore, Dr. Chaffee provides a similar overview, but utilizing primate models to explore the theory of the failure cascade leading to prefrontal circuit collapse in people with schizophrenia. The importance of using non-human primates is that prefrontal networks are similarly anatomically organized between monkeys and humans, with similar imaging tools used across species in a consistent developmental timeline. Tying these changes to behavioral outcome is vital and the authors highlight the opportunity for RDoC to more closely tie such neural developmental changes to outcome consistent across species.

From the approach of these research chapters, the authors cover a great deal of research and standard areas of assessment toward developing therapies for cognitive dysfunction in people with schizophrenia. Other avenues of research exist however, including focusing on the impact of substance use in people with schizophrenia from a developmental to treatment perspective. Dr. Khokar and colleagues describe this

research, noting that healthy people who initiated cannabis use at earlier ages exhibited poorer cognition, while cannabis use in people with schizophrenia has been associated with the exacerbation of symptoms, but better overall cognitive performance, including in earlier age of use. Animal studies are then described to attempt to provide directionality of these effects, including specific cannabinoid agents.

Another important research area for cognitive disruption in people with schizophrenia is that of neuroinflammation and immunity, led by Dr. Deakin and colleagues. They describe that despite hypotheses, increased levels of cytokines detectable in the prodromal period were unlikely to be the driver of cognitive dysfunction in people with schizophrenia. Specifically, multiple meta-analyses did not however reveal any link between cytokine levels with cognitive impairment in people with high risk. Thus, the authors conclude that neuroinflammation is unlikely to be a core feature of schizophrenia or a driver in cognitive dysfunction, instead proposing that such deficits arise as a convergence of genetic and immune-neurodevelopmental dysregulation.

Another key area of research that is of great importance is that of potential sex/gender differences that occur in schizophrenia and cognition in general, led by Drs. Freeman and Lee. Initial studies demonstrate comparable sex effects in people with schizophrenia to healthy populations across multiple domains and phases of the illness. Further questions remain unresolved however, which may provide clues between cognitive impairment and pathophysiological processes.

Often overlooked is the potential deleterious impact that current therapeutics may exert on cognitive functioning. Acetylcholine plays a major role in cognitive functioning and several antipsychotics exert anticholinergic effects. This potential anticholinergic burden effect is described by Dr. Joshi, as is future directions that can detail potential detrimental effects and future directions for research.

Finally, almost all of the cognitive research described above utilize visual stimuli, and in some cases auditory stimuli. Oft-overlooked, however, are the olfactory cognitive deficits that arise as a result of the disease. Given that olfactory functioning develops early and dysfunction is seen across psychiatric conditions, Dr. MacQueen describes domains affected and paradigms that can be used to assess such functioning. Furthermore, this research offers opportunities for cross-species translational testing given faster cognitive training for rodents using olfactory cues.

In aggregate, this book provides an overview of research into the cognitive deficits associated with schizophrenia, where possible tying this research together utilizing language from the RDoC initiative. Although focused on schizophrenia, this transdiagnostic approach also provides insight into platforms of research approaches that can be used to determine mechanisms and treatments for other disorders that also involve cognitive challenges, such as bipolar disorder with psychotic features and individuals with chronic depression.

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# Contents

# The MATRICS Consensus Cognitive Battery: An Update

**Keith H. Nuechterlein, Michael F. Green, and Robert S. Kern**

## Contents



**Abstract** Through a series of NIMH-supported consensus-building meetings of experts and empirical comparisons of candidate tests, the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) initiative

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developed a battery of standardized cognitive measures to allow reliable evaluation of results from clinical trials of promising interventions for core cognitive deficits in this disorder. Ten tests in seven cognitive domains were selected for the MATRICS Consensus Cognitive Battery (MCCB). The MCCB has now been translated into 39 languages/dialects and has been employed in more than 145 clinical trials. It has become the standard cognitive change measure for studies of both pharmacological and training-based interventions seeking to improve cognitive deficits in schizophrenia. We summarize its applications and its relationship to the subsequent development of the NIMH RDoC Matrix.

**Keywords** Cognition · Clinical trials · International · MATRICS · Schizophrenia

## 1 Background of the MATRICS Initiative and Its Consensus Cognitive Battery

The Food and Drug Administration (FDA) and the National Institute of Mental Health (NIMH) in the USA came to recognize in the initial years after 2000 that development of interventions to improve cognitive deficits in schizophrenia was a critical unmet need. Standardized procedures for evaluating potential new agents for this purpose were not available and were limiting development in this area. Cognitive deficits in schizophrenia were known to be prominent predictors of functional outcome, more than the severity of positive symptoms (Green 1996; Green and Nuechterlein 1999; Green et al. 2000), but effective interventions to improve these cognitive deficits were not available. Although a few early clinical trials of potential cognitive enhancers were beginning, the FDA was unwilling to approve any drug for improving cognition in schizophrenia without consensus on cognitive domains, measurement of cognition, and study design (Hyman and Fenton 2003; Marder and Fenton 2004). Thus, the NIMH invited applications for a contract to develop a consensus among experts from academia, NIMH, the pharmaceutical industry, and consumer advocacy on recommended research design and cognitive measurement procedures.

After a competitive application process, the NIMH awarded a contract to UCLA to launch the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Initiative with Stephen R. Marder, M.D., as PI. As part of the broader MATRICS process, study design recommendations were developed (Buchanan et al. 2005, 2011) and promising neuropharmacological targets were identified (Geyer and Tamminga 2004). Another key aspect of the MATRICS Initiative was to identify the separable dimensions of cognition in schizophrenia and to develop a consensus measurement instrument to detect cognitive improvement in these domains in clinical trials (Green et al. 2004). While the MATRICS process preceded the development of the RDoC framework for clinical research,

identification of separable cognitive domains within the MATRICS initiative served as one influence on the later content of the NIMH RDoC Matrix.

A Neurocognition Committee was formed with experts from academia, NIMH, and consumer advocacy, led by Co-Chairs Keith Nuechterlein and Michael Green. It included representatives from academia (Drs. Deanna Barch, Jonathan Cohen, Susan Essock, James Gold, Robert Heaton, Richard Keefe, and Helena Kraemer), NIMH (Drs. Wayne Fenton, Terry Goldberg, Ellen Stover, Daniel Weinberger, and Steven Zalcman), and consumer advocacy (Dr. Frederick Frese). The key separable domains of cognition relevant to clinical trials in schizophrenia were identified by integrating data from factor analytic studies (Nuechterlein et al. 2004) and a survey of experts (Kern et al. 2004). A consensus was reached on seven domains to be included in a cognitive battery (Green et al. 2004). The cognitive domains were speed of processing, attention/vigilance, working memory, verbal learning, visual learning, reasoning and problem-solving, and social cognition.

The criteria for selecting tests for the battery were also determined at an initial MATRICS consensus meeting of experts in multiple relevant fields (Green et al. 2004). They were high test-retest reliability, utility as a repeated measure, demonstrated relationship to functional outcome, potential changeability in response to pharmacological agents, and practicality and tolerability. In addition, given that the maximum length of a cognitive battery for clinical trials was believed to be 2 h, individual tests needed to require less than 15 min of administration time.

A series of consensus meetings among experts were held, typically involving more than 100 experts from academia, NIMH, industry, and consumer advocacy. Initially, over 90 tests were nominated as possible indices of the seven cognitive domains. Then, a series of steps were completed to reach a final battery of 10 tests representing the seven cognitive domains. Initial discussion of the suitability of each test for a clinical trials battery narrowed to the nominations to six or fewer tests per cognitive domain, often based on the administration time required or the practicality of training time or scoring. This initial review produced 36 candidate tests across the seven cognitive domains. Then, a database of existing test information relevant to the selection criteria was created for each test. A structured consensus process, the RAND/UCLA Appropriateness Method (Young et al. 2000; Fitch et al. 2001), was used by an expert panel to systematically evaluate the 36 tests. Based on a review of all relevant scientific evidence regarding the selection criteria, the RAND/UCLA method applied, iteratively, procedures to help increase agreement among members of the expert panel representing key stakeholder groups. This step led to the selection of the 20 most promising tests.

The final step in the selection process involved administering the 20 tests to 176 individuals with schizophrenia at five sites across the USA to directly compare the properties of these tests. A four-week follow-up assessment was completed with 167 of these participants to assess test-retest reliability, practicality of administration and scoring, and tolerability of the test with the participants. The final group of 10 tests was selected by the MATRICS Neurocognition Committee based on these data (Nuechterlein et al. 2008). A normative community sample of 300 individuals drawn from the same five sites, stratified by age, gender, and education, was also

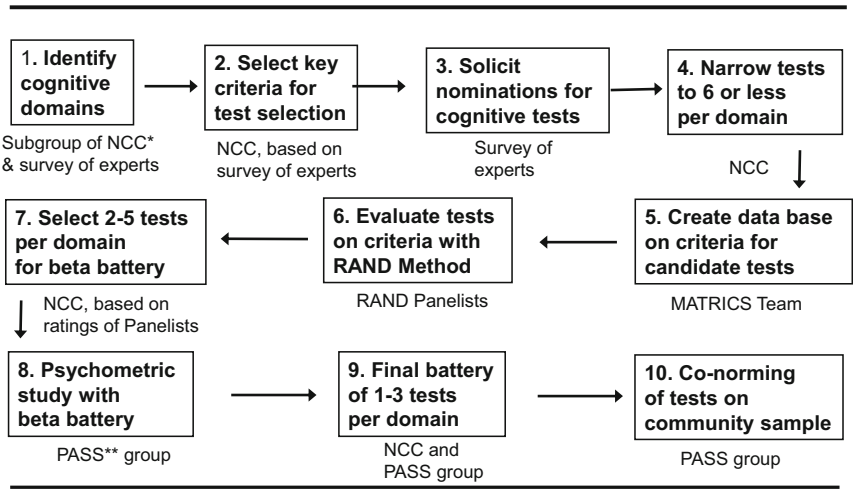


**Fig. 1** Steps to create the MATRICS consensus cognitive battery

administered the 20 tests to allow co-norming, which places each test on the same measurement scale and allows correction for demographic effects in the general population (Kern et al. 2008). Because the FDA indicated that a co-primary measure of everyday functioning or functional capacity would also be needed in clinical trials, candidate measures for this co-primary role were also administered to the schizophrenia participants and evaluated for their promise (Green et al. 2008). The steps to create the MCCB™ are summarized in Fig. 1.

A non-profit company, MATRICS Assessment, Inc., was formed to allow compilation of the 10 tests into a published battery, with licensing agreements with the individual copyright holders (Nuechterlein and Green 2006). A MATRICS Computer Scoring Program was developed to convert the test raw scores into T scores, cognitive domain T scores, and an Overall Composite T score, with options to correct for age and gender (recommended for schizophrenia) or age, gender, and education (for application to disorders that typically occur after educational periods are completed). Distribution of the battery was arranged with three psychological test corporations (Multi-Health Systems, Inc., Pearson, Inc., and Psychological Assessment Resources, Inc.).

## 2 Translation and Normative Data with the MCCB™ in Additional Languages

### *2.1 Translations*

It quickly became apparent that the application of the MCCB™ in large clinical trials of new agents for improving cognition in schizophrenia would require that it be

available in multiple languages, as many of these trials involve international data collection. Thus, a government-industry collaboration, MATRICS-CT (Co-primary and Translation), was formed soon after the completion of the MATRICS Initiative to fund the professional translation of the MCCB™ and the collection of normative data in six languages/dialects: Chinese, German, Hindi, Russian, Spanish for Spain, and Spanish for Central/South America.

MATRICS Assessment, Inc., supervised the translations using the following steps for each language (Hambleton et al. 2005). First, a professional translation company was selected and the English version of the tests and the MCCB™ Manual was provided to them. Second, two professional translators completed a forward translation of the test materials and the MCCB™ Manual chapters on administration and scoring. The two translators then reconciled their translations. A third professional translator then back translated the materials into English and checked for discrepancies from the original English version. After these translators reached consensus on a forward translation, the translation was provided to a psychologist or psychiatrist experienced with neuropsychological testing who was a native language speaker in the target language. That local professional expert reviewed the translation for tone and phrasing appropriate to a psychological testing situation. This feedback was provided to the professional translators, who adapted the translation accordingly.

The resulting refined version was then set into a PDF format and printed for pilot work. It was provided to a trained psychological testing professional in the target country to pilot test 3–5 schizophrenia patients or individuals with similar disorders. Feedback from this pilot work was used to determine whether any phrasing of instructions to patients was unclear. In addition, the results were scored and examined by the authors of this chapter to detect any unusual patterns that needed to be queried further. Once a final translated version was reached, a print-ready version of all materials was sent to a professional printer company and an initial batch of MCCB™ kits in the language were printed and assembled. The steps in translating and culturally adapting the MCCB™ are summarized in Fig. 2.

In addition to the professional translations that are appropriate for clinical trials and all other applications, MATRICS Assessment, Inc. also established a process by which individual academic researchers could obtain permission to translate the MCCB™ for their non-commercial research. This translation process also includes forward and back translation and review of the back translation by MATRICS Assessment, Inc., and test copyright holders, but does not involve the other steps. These translations are not commercially available and are not appropriate for commercial clinical trials. Academic research translations have been completed for some languages for which a professional translation has not been done, including Brazilian Portuguese. Other academic research translations have subsequently been replaced by professional translations.

The demand for translation of the MCCB™ into multiple languages has remained strong over the years since the initial publication of the English version in 2006 (see www.matricsinc.org). The MCCB™ is currently available in 39 languages (see Table 1).

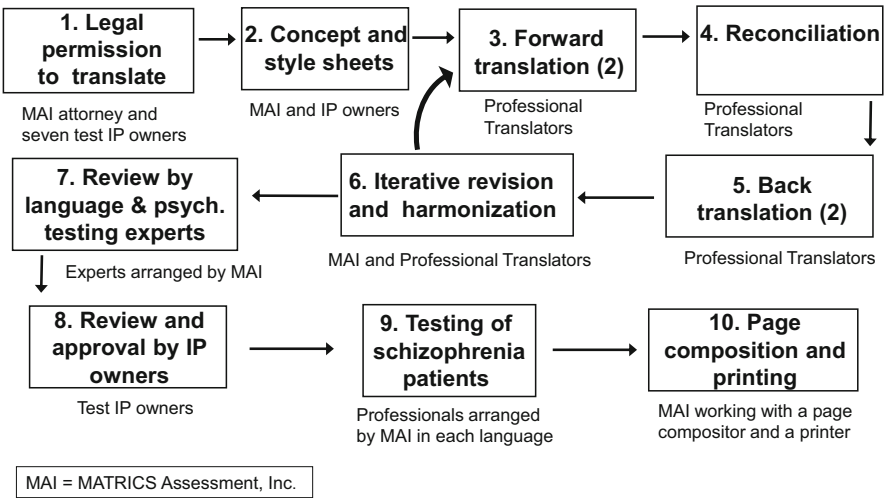


**Fig. 2** Steps in translation and cultural adaptation of the MATRICS consensus cognitive battery

**Table 1** Languages in which the MCCB™ is currently available

| Armenian (academic research only) | Greek | Portuguese – Brazil (academic research only) |
|---|---|---|
| Bulgarian | Hebrew | Portuguese – Portugal |
| Chinese – simplified | Hindi | Romanian |
| Chinese – traditional | Hungarian | Russian |
| Croatian | Italian | Serbian |
| Czech | Japanese | Slovak |
| Danish | Kannada | Spanish for Central and South America |
| Dutch | Korean | Spanish for Spain |
| English | Lithuanian | Swedish |
| English – Malaysia | Malay | Tamil |
| French | Marathi | Telugu |
| Finnish | Norwegian | Turkish |
| German | Polish | Ukrainian |

## *2.2 Community Norming in Other Languages*

For several of the MCCB™ translations that are most typically used in international clinical trials, community normative data have been collected through a process paralleling the norming of the English MCCB™ in North America. For each language, 200 to 300 community members stratified by age, gender, and education were administered the translated MCCB™, mainly with funding from the MATRICS-CT collaboration between NIMH and industry. The results were

analyzed by the MATRICS Assessment, Inc., team and T scores were created that parallel those for the English MCCB™. The MCCB™ Computer Scoring Program was updated to provide these T scores for Simplified Chinese, German, Hindi, Italian, Japanese, Russian, Spanish for Spain, and Spanish for Central/South America (Nuechterlein and Green 2016).

## 2.3 *International Scoring System for the MSCEIT Managing Emotions Branch*

Because the items in the social cognition test in the MCCB™, the MSCEIT Managing Emotions Branch, appeared to be less universal in cultural context than the other tests in the MCCB™, research was completed to evaluate the extent to which the frequency of alternative answers and their correlation with the total test score differed from the English version (Hellemann et al. 2017).

The MSCEIT Managing Emotions Branch uses a "consensus based" scoring method in which the score assigned to a response is the proportion of a population that selected that response in the normative sample. Thus, rather than a "correct" response, the scores reflect the extent to which a response agrees with the responses by community members. Multi-Health Systems, Inc., developed the original norms of the MSCEIT Managing Emotions Branch using a large sample ($N = 2{,}112$) of participants drawn from seven English-speaking countries.

To examine the degree to which responses of community members from other cultures differed from those in the English-speaking countries, we examined the individual item data from the community normative samples from China, India (Hindi), Japan, Russia, Spain, and Central and South America. Each sample was stratified by age, sex, and education according to its region's population. We used a measure known as L1 (Manhattan norm) to measure the discrepancies across cultures/countries. It is defined as the sum of the absolute differences between the percentages of choices for each of the response options (Hellemann et al. 2017). We also examined whether items were reverse scored across cultures/countries. That is, whether a response considered to be an effective handling of certain emotions in one culture was usually considered to be an ineffective method in another culture.

Three items were found to be reverse scored across cultures, while three additional items had high discrepancy scores. Thus, 6 of 29 items were excluded from the International MSCEIT Branch 4 Scoring Program. Correlations between the original scores and those generated by the international scoring system were high (generally $r > 0.80$) for each country, but the international scoring produced less discrepancy from country to country (Hellemann et al. 2017). The International MSCEIT Branch 4 Scoring Program is therefore recommended for non-English-speaking applications of the MCCB™.

## 3 Development of the Neurocognitive Composite Score

The growing awareness that neurocognition (non-social cognition) and social cognition are separable dimensions (Fett et al. 2011; Lee et al. 2013; Green et al. 2019) led us to develop a composite score that summarizes performance across the six neurocognitive domains. Some interventions might impact social cognition and non-social cognition differently, or might target one or the other, such as the effect of oxytocin on social cognition (Davis et al. 2014). To allow investigators to examine non-social cognition only, we developed the Neurocognitive Composite score, which is distributed as a T score in the normative samples based on the six non-social cognitive domains. We incorporated an option to generate the Neurocognitive Composite score into the 2016 version of the MCCB™ Computer Scoring Program. This additional composite score was reviewed and approved by the MATRICS™ Neurocognition Committee.

## 4 Website for Downloading the MCCB™ Computer Programs

Three computer programs were supplied on CDs with the original MCCB™ kit (Nuechterlein and Green 2006): the CPT-IP administration and scoring program, the MSCEIT Branch 4 Scoring Program, and the MCCB Computer Scoring Program. With the multiple translations of the MCCB™, the translated directions to subjects were added to the CPT-IP.

MATRICS International Version 2 program. In 2016, the International MSCEIT Branch 4 Scoring Program was added to the CDs. As PC laptops increasingly were designed without built-in CD/DVD drives and were often the most convenient way to administer the CPT-IP and score the MCCB, particularly in multisite clinical trials, the demand for downloadable MCCB programs grew.

As a result, we worked with a website developer to make it possible for those who purchased an MCCB™ kit to download the four MCCB computer programs as an alternative to loading them from CDs. Starting in 2021, this became a standard feature of the MCCB™.

## 5 Applications of the MCCB™ in Clinical Trials

The primary goal for the development of the MCCB™ was to provide a standardized cognitive battery for use in clinical trials that would allow cognitive gains to be compared across trials (Green et al. 2004; Kern et al. 2008; Nuechterlein et al. 2008). The MCCB™ has been very successful in this regard. The FDA has called the MCCB™ the gold standard for measuring cognitive change in clinical trials for

schizophrenia. A search of ClinicalTrials.gov for the term MATRICS yields 245 studies, which documents the overall impact of the MATRICS Initiative on clinical trials of potential interventions to improve cognition in severe mental disorders. Although not all studies used the abbreviation MCCB in their study descriptions, a ClinicalTrials.gov search for MCCB indicates that at least 145 clinical trials did include this consensus cognitive battery. The fact that these studies have been conducted in many different countries is evidence that the MCCB™ is widely accepted as the standard battery for clinical trials internationally. Some studies of bipolar disorder and other severe mental illnesses are also among the applications listed in ClinicalTrials.gov.

## *5.1 Pharmacological Clinical Trials with the MCCB*

In the years since the MCCB™ was published in 2006, many clinical trials have been completed to evaluate the safety and efficacy of potential pharmacological cognitive enhancers for schizophrenia. A 2018 meta-analysis examined results from 93 randomized clinical trials that evaluated cognitive improvement with neuropsychological tests, 76 of which were reported from 2007 through 2017 (Sinkeviciute et al. 2018). Although not all 76 clinical trials reported since the publication of the MCCB™ used this battery to measure cognitive change, the MCCB™ has become the most common choice as the primary cognitive outcome measure, either focusing on the Overall Composite T Score or, less frequently, on one of the cognitive domain T scores from the MCCB™. Even when the MCCB™ is not used in the earliest phases of clinical trials, it is usually adopted in later phases due to its acceptance as the gold standard by the FDA.

After initial enthusiasm for examining new agents that targeted a wide range of neurotransmitter systems (Geyer and Tamminga 2004; Geyer and Heinssen 2005), most randomized clinical trials have unfortunately yielded negative results. The Sinkeviciute et al. (2018) meta-analysis found that the effect size across all cognitive enhancers in the 93 studies, with 5,630 participating patients, was positive and significant, but quite small (Hedge's $g = 0.10$, $p = 0.023$). The most promising pharmacological targets were the glutamatergic system (overall cognition Hedge's $g = 0.19$, $p = 0.01$; working memory $g = 0.13$, $p = 0.04$) and cholinesterase inhibitors (working memory $g = 0.26$, $p = 0.03$). A common pattern was positive results in early Phase II trials followed by failure to replicate the positive findings in larger late Phase II trials or Phase III trials. This pattern led to a search for factors in research design, sample selection, and cognitive measurement that might be limiting detection of a cognitive signal (Green et al. 2019; Keefe 2019).

The clinical trials with new pharmacological agents targeting cognition in schizophrenia since 2018 have recently been reviewed by Horan et al. (in press). Of the 9 trials that they list, 8 use either the MCCB Overall Composite or Neurocognitive Composite Score or the MCCB Working Memory domain score as their primary cognitive endpoint. While it remains the case that no drug for enhancing cognition

associated with schizophrenia has been approved by the FDA, and 2 of the 9 trials are completed with negative results, one completed trial was positive for MCCB™ composite gains and 6 remain active at this point (Horan et al. in press). The most promising compound at this time is Boehringer Ingelheim's glycine transporter-1 (glyT1) inhibitor, BI 425809, which is currently in large Phase III trials after positive MCCB Overall Composite results in a multisite Phase II trial. The FDA granted BI 425809 Breakthrough Therapy Designation for cognitive impairment associated with schizophrenia in May 2021 (Horan et al. in press). Another glutamatergic drug, BIIB-104, a positive allosteric modulator (PAM) of the AMPA receptor (AMPAR), is currently being examined in a phase IIb study by Biogen. The cognitive target in that case is the MCCB Working Memory domain score.

## 5.2 *Psychometric Properties of the MCCB™*

As the earlier negative results of clinical trials of potential pharmacological cognitive enhancers multiplied, one concern was whether the psychometric properties of the MCCB™ were leading to too much measurement noise, practice effects, and ceiling effects, thereby reducing sensitivity to the drug effects. These concerns have been allayed by careful examination of the psychometric properties of the battery. First, the selection criteria for tests in the MCCB™ emphasized the need for high test-retest reliability, utility as a repeated measure, and potential changeability in response to pharmacological agents (Nuechterlein et al. 2008). In the 5-site psychometric study with 167 schizophrenia patients assessed twice 4 weeks apart, the selected individual tests had high test-retest reliability (ICC of 0.68–0.85) and the Overall Composite Score had an ICC of 0.90. In addition, the effect sizes for practice effects for the individual tests ranged from Cohen's $d = 0.00$ to 0.22 (Nuechterlein et al. 2008). Those data also showed that the obtained scores were rarely or never at the floor or ceiling of the tests. Thus, the initial data supporting test selection indicated high test-retest reliability, small practice effects, and absence of floor or ceiling effects.

A question remained, however, about the psychometric properties of the MCCB™ in actual clinical trials. This issue was well addressed by Keefe and colleagues through the examination of data from a 29-site clinical trial with 323 outpatients with schizophrenia (Keefe et al. 2011). Patients were assessed at screening and a median of 15 days later at baseline. The test-retest reliability of the Overall Composite Score was very high (ICC = 0.88). Furthermore, the practice effect for the composite score was quite small (Cohen's $d = 0.18$) and not statistically significant. Individual cognitive domain T scores were also generally above ICC of 0.70, except for Verbal Learning (0.58) and Visual Learning (0.65) and only Reasoning and Problem-Solving showed a significant practice effect (Cohen's $d = 0.14$). When one considers that the mean Overall Composite T score for these schizophrenia patients was about 25 (general population mean = 50 with SD = 10) and that the practice effect is about 2T scores from first to second administration, it

becomes clear that practice effects are very small and that ceiling effects are not suppressing drug effects. Furthermore, any practice effects would be maximum from first to second administration, so further repeated administrations would be even less impacted by practice.

### *5.3 Clinical Trials with Training-Based Interventions*

The sensitivity of the MCCB™ to cognitive change becomes clear when the results of clinical trials with cognitive remediation and other training-based interventions are considered. The popularity of the MCCB™ to evaluate cognitive effects for training-based interventions is evident based on a search of ClinicalTrials.gov. Forty-three trials of cognitive training use either the MCCB Overall Composite score or one of its cognitive domain scores to evaluate the efficacy of the intervention. Recently physical exercise has become another training-based intervention that is being actively evaluated for improving cognition in psychosis. ClinicalTrials.gov lists nine studies of physical exercise effects on the MCCB, four of which examine physical exercise combined with cognitive training. One additional study is examining the impact of mindfulness training on cognition using the MCCB.

Of the 43 cognitive training studies, only nine have yet posted results and most are ongoing. A series of studies completed by Vinogradov, Fisher, and colleagues at UC San Francisco using a slightly modified MCCB have demonstrated significant differential cognitive improvement in schizophrenia with Posit Science auditory processing modules (now part of BrainHQ) compared with a computer games control group. The effect sizes have been medium to large for the global cognition score with patients with multi-episode schizophrenia ($d = 0.86$) (Fisher et al. 2009), relatively recent-onset schizophrenia ($d = 0.73$) (Fisher et al. 2015), and clinical high risk for psychosis (Loewy et al. 2016). When these modules were administered remotely with relatively recent-onset patients, the improvement was present 6 months after training (Loewy et al. 2022). A similar large differential effect of Posit Science Brain Works modules versus nonspecific computer games was demonstrated in bipolar patients ($d = 0.80$) for the MCCB Overall Composite Score (Lewandowski et al. 2017). Using a different set of cognitive training modules drawn from NET (Bell et al. 2001) and NEAR (Medalia et al. 2000, 2001), Nuechterlein and colleagues at UCLA showed that first-episode schizophrenia outpatients had substantial differential MCCB Overall Composite gains (equivalent to $d = 0.72$) with cognitive training compared to a healthy behavior training comparison group (Nuechterlein et al. 2020) when medication adherence was covaried. This study also demonstrated generalization of effects to everyday work/school functioning (equivalent to $d = 0.78$).

One limitation of the cognitive training literature thus far has been to show similar substantial MCCB™ improvements in large multisite studies. Thus, a multisite Posit Science study (Mahncke et al. 2019) of 150 schizophrenia patients failed to find a differential cognitive effect of cognitive training versus computer games using the

MCCB Overall Composite Score. Limitations in patient treatment engagement were a possible contributor. Similarly, a multisite study in which all schizophrenia patients were first stabilized on lurasidone before randomization did not find significant differential MCCB gains from randomization to the study endpoint (Kantrowitz et al. 2016), although substantial cognitive improvements during the lurasidone stabilization period complicated the analyses. Thus, the sensitivity of the MCCB™ to cognitive gains produced by cognitive training is well demonstrated by well-controlled studies at single academic sites. Why multisite studies do not reveal the same strong effects needs further examination, as these factors may be impacting both pharmacological and cognitive training multisite clinical trials.

Clinical trials of physical exercise have also demonstrated that the MCCB™ can sensitively detect cognitive gains. Kimhy and colleagues (2015) showed that an X-Box aerobic exercise program produced large cognitive improvements ($d = 0.93$) on the MCCB Overall Composite Score. Furthermore, Nuechterlein and collaborators (2022) demonstrated that adding an aerobic exercise program to cognitive training could produce a large boost in the magnitude of cognitive gain (equivalent to $d = 0.86$) in 3 months and generalization to larger work/school functioning gains (equivalent to $d = 1.06$) by 6 months compared to cognitive training alone.

## 6 Applications of the MCCB™ within Psychopathology Research

### *6.1 Factor Analytic Studies of the MCCB™*

Several studies have reported results of factor analyses of the MCCB™. While the number of factors derived from the 10 tests of the final MCCB™ has varied somewhat, the most common result has been three factors (Burton et al. 2013; Lo et al. 2016; Mohn et al. 2017; Kuo et al. 2020). Usually these factors represent processing speed, attention/working memory, and learning (Burton et al. 2013; Lo et al. 2016; Kuo et al. 2020), but sometimes a slightly different structure (Holmen et al. 2019). The major limitation of these factor analytic studies is that they include only the 10 scores from the final MCCB™. Most of the seven cognitive domains in the MCCB™ are represented by only one test to keep the battery as brief as possible for clinical trials. However, at least two measures of a hypothesized dimension are generally considered necessary to identify a factor through factor analysis. Thus, the confirmatory factor analysis by McCleery and colleagues (2015) is distinctive in that it used the beta battery from the MCCB development process (Nuechterlein et al. 2008), which includes at least two measures of each hypothesized cognitive domain. McCleery et al. (2014) confirm that a seven-factor solution is the best fit, significantly better than a single factor, three correlated factors, or a hierarchical model. These results support the seven cognitive domains that were the basis for the development of the MCCB™.

## 6.2 Profile of Cognitive Deficits in Schizophrenia

Using the original five-site sample of schizophrenia patients and healthy adults which led to the selection of the final 10 tests in the MCCB™, Kern and colleagues demonstrated that each of the seven domain T scores was very sensitive to cognitive impairment in schizophrenia, with T scores ranging from 33 to 39 (community mean of 50 with SD of 10) (Kern et al. 2011). Speed of processing and working memory was most impaired, while reasoning and problem-solving was least impaired. As Kern et al. (2011) discuss, the lower scores for speed of processing and working memory might be due to the fact that these domains are measured by more than one test in the MCCB, which would tend to increase their sensitivity to deficits. McCleery and collaborators compared this sample of multi-episode schizophrenia patients (mean age of 44 years) with a first-episode schizophrenia sample (mean age of 22 years) to examine whether evidence of progression of cognitive deficit was present (McCleery et al. 2014). They found that the level of impairment was comparable for most cognitive domains, but working memory and social cognition deficits were significantly less severe in the first-episode patients.

Subsequent examinations of the profile of cognitive deficits in schizophrenia across domains using translations of the MCCB have confirmed that the deficits are present in all seven cognitive domains in countries outside the USA, usually between one and two standard deviations below the healthy community mean (Rodriguez-Jimenez et al. 2015; Fonseca et al. 2017; Mucci et al. 2018; Bezdicek et al. 2020). When Spanish samples of multi-episode and first-episode schizophrenia patients were compared, the deficits of first-episode patients were again generally comparable, but in this case verbal and visual memory and attention/vigilance were somewhat less severely impaired than in multi-episode patients (Rodriguez-Jimenez et al. 2019). Thus, the sensitivity of the MCCB™ to cognitive deficits in schizophrenia is clear across multiple languages and cultures. The specific cognitive domains that may show progression in the severity of deficits from the first episode to later stages of schizophrenia need further investigation.

## 6.3 Sensitivity of MCCB™ to Cognitive Deficits in Biological Relatives and Familial Aggregation

The Italian Network for Research on Psychosis administered the Italian translation of the MCCB to 852 outpatients with schizophrenia, 342 unaffected relatives, and a normative Italian sample of 774 healthy subjects (Mucci et al. 2018). They found that the schizophrenia patients were one to two standard deviations below the normative mean in each cognitive domain and the biological relatives were about 0.5 standard deviations below the normative mean. Relatives were significantly below the normative mean in each domain except social cognition, but they had significantly less severe deficits than the patients in each domain. Proband scores

significantly predicted their relatives scores for every domain except visual learning (Mucci et al. 2018). Thus, the MCCB™ detects subtle cognitive deficits in biological relatives of schizophrenia probands which show significant familiality.

The MATRICS initiative also was one influence on the later development of the RDoC approach to NIMH clinical research. The emphasis on consensus processes was also a prominent feature of the construction of the NIMH RDoC Matrix. The focus on establishing cognitive domains of importance in major psychopathology was further elaborated in the NIMH RDoC Matrix. Some domains in the NIMH RDoC Matrix are similar to those selected by the MATRICS initiative (Green et al. 2004; Nuechterlein et al. 2004), designated as either Cognitive Systems (i.e., attention, working memory, declarative memory) or Social Processes (social communication, perception and understanding of self, perception and understanding of others).

## 7 Summary

The MCCB™, developed through multiple steps by a wide range of experts participating in the NIMH MATRICS Initiative, has had a major impact on the measurement of cognitive deficits in schizophrenia and particularly on the evaluation of cognitive change in clinical trials.

The MCCB™ has been applied in psychopathology research to examine the separable cognitive dimensions in individuals with schizophrenia, the profile of deficits across those cognitive domains in patients with schizophrenia and their biological relatives, and the familiality of these cognitive deficits. When multiple tests of each hypothesized domain are included, the seven separable domains underlying MCCB™ development are confirmed. The mean scores of samples of patients with schizophrenia are one to two standard deviations below community norms, their biological relatives are only about a half standard deviation below community norms, and there is a significant familiality of cognitive performance.

The development of the MCCB™ has allowed comparisons of the degree of cognitive improvement achieved in many different clinical trials, as desired by the FDA. The translation of the MCCB™ into more than 30 languages has greatly facilitated international clinical trials of interventions to improve cognition in schizophrenia. The co-norming of the MCCB™ tests in multiple languages and cultures has further aided international use of the battery. While most trials of possible pharmacological cognitive enhancers have thus far been negative, some promising new compounds are currently being tested. Clinical trials of cognitive training and physical exercise programs have shown that it is possible to achieve medium to large cognitive gains in schizophrenia and these can be sensitively detected by the MCCB™. The applications of the MCCB™ in clinical trials can be expected to continue expanding as it has become the primary tool through which the promise of interventions to improve the core cognitive deficits in schizophrenia is judged.

While the MATRICS initiative and development of the MCCB preceded the development of the RDoC approach to clinical research, its emphasis on multiple cognitive domains and consensus among experts was an influence on the later construction of the NIMH RDoC Matrix. Some dimensions identified for the MCCB (i.e., attention, working memory, learning, social cognition) are represented in the NIMH RDoC Matrix, sometimes using different terms. Additional influences on the NIMH RDoC Matrix came from the later Cognitive Neuroscience Treatment Research to Improve Cognition in Schizophrenia (CNTRICS) meetings (Barch et al. 2009; Carter et al. 2008). The CNTRICS meetings led to additional distinctions among different cognitive control processes and working memory components that were derived from the neuroscience literature rather than from factor analytic studies of cognitive dimensions in schizophrenia. The processes identified by the CNTRICS meetings and incorporated into the NIMH RDoC Matrix emphasize cognitive components that can be disassociated from each other rather than combined into broader composite scores. Thus far the broad composite scores have been adopted as the primary outcome by most clinical trials of cognitive enhancers to maximize sensitivity to cognitive gains that are correlated. Targeted interventions might address only certain cognitive processes that are dysfunctional in schizophrenia, as both the individual MCCB cognitive domains and the tasks developed from the CNTRICS initiative allow for this possibility. Until this point less effort has been devoted to trials of such more targeted cognitive interventions.

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