Cognitive Neuroscience-Based Approaches to Measuring and Improving Treatment Effects on Cognition in Schizophrenia: The CNTRICS Initiative

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The goal of this article is to discuss ways to further improve the search for potentially procognitive agents that could be used to enhance cognition and functional outcome in schizophrenia. In particular, we focus on the potential advantages to this process of using a contemporary, cognitive neuroscience-based approach to measuring cognitive function in clinical trials of procognitive agents in schizophrenia. These tools include computer-administered tasks that measure specific cognitive systems (such as attention, working memory, long-term memory, cognitive control) as well as the component cognitive processes that comprise these more overarching systems. The advantages of using these tools include the ability to identify and use homologous animal and human models in the drug discovery and testing process and the ability to incorporate noninvasive functional imaging measures into clinical trial contexts at several different phases of the drug development process. However, despite the clear potential advantages to using such methods, a number of barriers exist to their translation from basic science tools to tools for drug discovery. We discuss the development and implementation of a new project, Cognitive Neuroscience Treatment to Improve Cognition in Schizophrenia, designed to identify and overcome these barriers to the translation of cognitive neuroscience measures and methods into regular use in the drug discovery and development process of cognition-enhancing agents for use in schizophrenia.

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An important element of the legacy of Wayne Fenton, MD, is a bold research agenda focused on improving the lives of people with serious mental disorders. Wayne and others took note of the growing literature showing a strong relationship between the level of cognitive impairment and poor functional outcome in individuals with schizophrenia,[1,2] coupled with the limited response to this aspect of the illness to available antipsychotic medications. These observations led to an enhanced priority for developing targeted therapies for cognition in schizophrenia. However, many barriers existed to realizing this crucially important goal, and a number of research and public policy programs have started to help overcome these barriers and to realize Wayne Fenton's vision.

Measurement of Treatment Effects on Cognition in Schizophrenia

The field has achieved a rapidly growing understanding of the neurobiology and neuropharmacology of cognition and has identified many molecular targets with the potential to enhance cognitive processing in schizophrenia and other psychiatric disorders.[3–9] However, despite this growing knowledge, there was no established mechanism for developing cognitive enhancing drugs for schizophrenia. To address this, the Measurement of Treatment Effects on Cognition in Schizophrenia (MATRICS), led by Steven Marder and Michael Green[10,11] from University of California, Los Angeles (described in another article in special issue), took the process into the fast track. MATRICS brought together academia, the pharmaceutical industry, and the Food and Drug Administration (FDA) to: (1) identify cognitive targets in schizophrenia, (2) identify promising molecular targets of that could enhance cognition, and (3) develop a process by which new therapeutic agents could be approved for the treatment of schizophrenia. Through the MATRICS process, the viability of the development of targeted treatments for cognition in schizophrenia was firmly established and a set of instruments, the MATRICS cognitive battery, was developed for use in

clinical trials of potentially procognitive agents in schizophrenia.

One of the challenges that the MATRICS faced and overcame was the need to produce a consensus-based set of cognitive measures in a rapid time frame, so that industry and academia could have a battery that was recognized by the FDA as valid measures of cognition in clinical trials. Because of this rapid time frame, the MATRICS battery selected only well-standardized tests with well known, strong measurement properties (such as test-retest reliability, low practice effects, etc). As such, the approach to measurement included in the MATRICS cognitive battery primarily reflects the experience in the field with largely pen and paper clinical neuropsychological tests developed for and validated in the clinical trials of atypical antipsychotics during the 1990s. Other types of measures, derived more from a human and/or animal cognitive neuroscience tradition, were considered for inclusion in the MATRICS battery. However, because these measures did not have already established or well-understood measurement properties and the MATRICS project could not wait for the development of such data, such cognitive neuroscience-based measurement tools were not included in the MATRICS battery. Nonetheless, during the course of the MATRICS process, and formally in the sixth and final meeting (the New Approaches Conference [NAC]), much discussion occurred regarding the potential benefits of using a different approach to the measurement of cognition in schizophrenia in drug discovery—namely tasks and tools derived from cognitive neuroscience.[12] It was out of this NAC meeting that the Cognitive Neuroscience Treatment to Improve Cognition in Schizophrenia (CNTRICS) initiative evolved.

Benefits of Applying Cognitive Neuroscience–Enhancing Cognition in Schizophrenia

During the New Approaches meeting, the potential benefits of pursing a cognitive neuroscience-based approach to conceptualizing and measuring cognition in schizophrenia were generally acknowledged and elucidated. To understand and articulate these potential benefits, it is useful to first outline what we mean by the cognitive neuroscience approach. We would argue that the cognitive neuroscience approach involves 5 key characteristics: (1) measuring specific cognitive processes or mechanisms that may contribute to one or more domains of cognitive or affective function, (2) identifying the neural systems that support such specific psychological mechanisms, (3) bringing to bear both animal and human research to identify neural substrates of specific processes, (4) developing and using cognitive tasks and paradigms that attempt to isolate specific processes, and (5) incorporating tools that measure the associated neural systems as well as the observable behaviors (eg, evoked

response potentials [ERPs], functional magnetic resonance imaging [fMRI], magnetoencephalography [MEG], magnetic resonance spectroscopy [MRS], etc)

Measuring the function of specific cognitive systems that are linked to specific neural systems using a cognitive neuroscience approach offers unique advantages, especially for translational research. One of the key advantages is the ability to use the results of animal as well as human studies to *identify* molecular targets that modulate cognition. Many of the targetable systems, such as long-term and working memory, attention, perceptual processing, and cognitive control are conserved across many mammalian species and measurable using parallel versions of experimental cognitive tasks. The last 20 years has given rise to a number of excellent examples of domains in which the cross fertilization of human and animal research has lead to novel insights into the neural mechanisms that support specific cognitive functions and the potential neuropharmacological targets for procognitive agents. One obvious example is the domain of working memory, particularly spatial working memory. Working memory refers to the ability to temporarily store and manipulate information.[13,14] It is considered a core cognitive deficit in schizophrenia by many researchers,[15–17] and deficits in this cognitive domain may also serve as an endophenotypic marker of risk for schizophrenia.[18] The seminal work of researchers such as Pat Goldman-Rakic[19,20] has generated a wealth of information about the neural circuits and neurotransmitters that support working memory and has enhanced our understanding of the neuromodulation of working memory. This enhanced understanding includes information about the role of different neurotransmitter systems (eg, dopamine, norephinephrine, glutamate)[4,21–23] that may interact in important ways[21] as well as the differential roles of specific receptor types (eg, D1 vs D2)[24] that point directly to new directions for targeted drug development. In addition, the animal research has highlighted the complexity of understanding neurotransmitter effects on working memory and prefrontal function, including identifying issues related to an ''inverted U''-shaped relationship between D1 modulation and prefrontal function.[22] Further, the body of animal research in this domain has led to numerous studies in humans that both confirm and extend our understanding of the neuropharmacology of working memory in humans,[25] though clearly further research work in humans with more targeted agents is needed.

A second example is the domain of episodic or declarative memory or the ability to learn and retrieve new information. Episodic memory deficits are also key cognitive impairments in schizophrenia[26] that may also serve as an endophenotypic marker of risk for this illness.[27,28] This is again a domain in which a large body of parallel animal and human cognitive neuroscience research has identified the neural circuits that support specific aspects

of episodic memory, as well as the differential roles of particular neurotransmitter systems such as acetylcholine and glutamate.[29,30] Importantly, the research stemming from the cognitive neuroscience literature has emphasized the fact that different aspects of episodic memory (eg, familiarity, recollection) may rely on different neural circuits[31] and that measures of episodic memory that help to isolate such subprocesses may more closely map to specific neural circuits and neurotransmitter systems. Much research in cognitive neuroscience has focused on developing such selective measures of different aspects of episodic memory. As such, the application of such measures to studies of cognition-enhancing agents in schizophrenia may help to reveal positive effects on specific aspects of episodic memory in this illness.

A second key advantage of the cognitive neuroscience approach is the ability to use the results of animal as well as human studies to *test* molecular targets that modulate cognition, by using homologous animal and human models. In other words, the use of homologous human and animal paradigms could enhance the likelihood that agents that improve cognition in the animal domain will lead to positive results in human clinical trials. This translation is obviously the easiest, both in terms of face validity and empirical support, when comparing nonhuman primate and human paradigms, such as those that have been used to study working memory (eg, oculomotor-delayed response). However, nonhuman primate models are less practical for use in early drug discovery and testing, where rodent models are needed. Thus, domains in which validated homologous rodent models are available would vastly aid in the development and testing of novel procognitive agents. We should note that while the use of parallel rodent/human models is an area that in some sense holds the most promise in terms of treatment development for schizophrenia, it is also one that faces a number of challenges.[23] As noted by numerous researchers, rodent brains are missing many key features of human neuroanatomy and function. As such, it is not always clear that animal paradigms designed to measure the same functions as assessed by human paradigms actually do capture the same constructs and cognitive processes.[23] However, to the degree that valid homologies do exist, the application of the cognitive neuroscience approach testing potentially procognitive agents will greatly facilitate multiple stages of the process.

A third advantage of the cognitive neuroscience approach is that many of the paradigms developed in this field have become widely used during noninvasive functional imaging studies using methods such as fMRI, ERPs, or MEG. Such noninvasive imaging studies have been used to further enhance our understanding of the nature of human cognitive and emotional processing and may be used in clinical studies to clarify the nature of cognitive deficits in schizophrenia and their neural corre-

lates. Pharmacological fMRI, the measurement of drug effects on activity in brain circuits during cognitive and emotional processing, has been increasingly applied to yield new insights into the mechanisms of drug actions in the brain.[32] There are at least 3 ways in which such methods could help facilitate testing the effects of procognitive drugs. The first way is by helping to identify and clarify the mechanisms by which the drugs are working, both in terms of their site of action and the time course or dynamics of their effects. The second way is perhaps less scientifically invigorating, but equally important, which is to demonstrate that the drug reached the brain, so that null results can be more definitely interpreted as a lack of effect, rather than a failure to cross the blood-brain barrier or reach the brain targets of interest. A third way in which the use of such methods could enhance drug discovery is by helping to identifying which individuals will eventually benefit behaviorally from cognition-enhancing agents. For example, individuals with schizophrenia may show cognitive deficits in a specific domain (eg, episodic memory) for different reasons or due to different types of neurobiological deficits (eg, deficits in prefrontal vs hippocampus-mediated functions). Functional imaging measures could help to determine whether individuals with similar behavioral profiles, but with different patterns of functional activation deficits, benefit more or less from the same agent. As another example, measures of functional brain activation taken after acute dosing could be used as predictors of eventual behavioral changes with chronic treatment. These technological innovations in the measurement of cognition in the human brain hold great promise to enhance translational research and to accelerate effective drug development for impaired cognition in schizophrenia. However, this approach has been untested in large-scale clinical trials to date, and several major pragmatic limitations to their use in large-scale studies were identified at the New Approaches meeting.

A fourth advantage of the cognitive neuroscience approach is that it may provide measures that, while not process pure, more effectively isolate constructs tied to specific neural systems or specific neurotransmitter functions. As noted above, cognitive neuroscience research is increasingly demonstrating that broad cognitive domains such as working memory, episodic memory, attention, and executive function comprised multiple subcomponents that may map to different neural circuits and be influenced in different ways by pharmacological manipulations.[33] Measures from other traditions that tap many different processes simultaneously (eg, the Wisconsin Card Sorting Task, Trail Making Test, etc, digit symbol substitution test) can be very sensitive to cognitive dysfunction in schizophrenia[34] but may be less helpful for understanding the specific nature of cognitive deficits,[35] for identifying useful drug targets, or for assessing change in specific cognitive functions.

Barriers to Translating Cognitive Neuroscience Methods

The discussions that occurred as part of the New Approaches Conference identified a number of important barriers to incorporating methods from cognitive neuroscience into the clinical trials domains. The first barrier was that there was no broad consensus regarding the cognitive processes or mechanisms that should be targeted for drug development in schizophrenia. The MATRICS faced this same barrier and used a factor analytic approach to identifying putatively separable cognitive domains to be assessed in schizophrenia. While this is a reasonable starting point, it did not take into account whether or not these domains or dimensions have been validated in terms of our understanding their neural circuitry, and it did not take into account the strong possibility that the broad cognitive domains assessed in the MATRICS battery actually be parsed into more biologically meaningful processes. The second barrier was that there are few standardized versions of the tasks used in cognitive neuroscience. In other words, a number of different researchers may use similar but nonidentical tasks to measure the same cognitive construct. Although these tasks might be similar (eg, different versions of oculomotor-delayed responses tasks, different versions of relational binding tasks), they could also vary widely in potentially important characteristics such as number of trials and frequency of different trial types, the types of conditions included. As such, some consensus was needed in terms of developing standardized version of validated tasks so that further testing could occur on a common set of paradigms. Finally, while there has been a good deal of experimental work using measures from cognitive neuroscience in behavioral and neuroimaging studies of schizophrenia, relatively little is known regarding the measurement properties of these tasks. For example, little is known about test-retest reliability, practice effects, or floor and ceiling effects in relevant populations for paradigms from the cognitive neuroscience literature. This is not surprising because these measurement properties have necessarily been seen as important to basic human and animal cognitive neuroscientists, and research focused on establishing such properties has not been part of their scientific agendas. However, such properties are critical for understanding the feasibility of using such measures in a clinical trial context.

Cognitive Neuroscience Treatment Research to Improve Cognition in Schizophrenia

In consultation with Wayne Fenton and other members of the Adult Translational Research and Treatment Development Branch of the National Institute of Mental Health, we proposed the CNTRICS initiative (http://www.cntrics.ucdavis.edu), which has as its goal to formally address the above limitations and to move the field one step closer to being able to fully integrate the tools and constructs of cognitive neuroscience into translational research focusing on developing therapies that target impaired cognitive and emotional processing in schizophrenia. The initiative has 3 aims, which will be addressed during 3 meetings over an 18-month period. Prior to each meeting, a series of web-based surveys will shape the agenda of each meeting. The first meeting "Cognitive Constructs" was conducted in February 2007 in Bethesda, MD.

The first aim is to identify a set of cognitive constructs that should be targeted for method translation and treatment development in schizophrenia. To aid in this process, we used an on-line survey process to first develop a set of criteria to use when selecting cognitive constructs. These criteria obviously not only included relevance to schizophrenia and understanding functional outcome in this disorder but also emphasized the advantages of the cognitive neuroscience approach, including validation in terms of both cognitive and neural systems, amenability for use in functional imaging, and the availability of homologous animal models. These criteria were then used, in a second on-line survey, to develop an initial list of candidate constructs from 6 broad cognitive domains: (1) working memory, (2) episodic memory, (3) attention, (4) executive function, (5) perception, and (6) social cognitive and affective processing. The mechanisms to be targeted were identified using input from experts in basic cognitive and affective neuroscience, as well as the clinical cognitive neuroscience of schizophrenia, and we developed a consensus based on input from individuals with backgrounds in both clinical and basic research and who were from both academia and industry. During the meeting, experts in the basic cognitive neuroscience of each of these domains provided an overview of the "state-of-the-art" in their respective fields. These overviews were followed by intensive discussion in smaller groups of experts from both the basic and clinical sciences (and both academia and industry) as to which constructs/processes within a domain best met the relevant criteria for targeted method translation. The results of this meeting, including the criteria developed through the survey processes and cognitive processes recommended for targeted method translation and drug development, are available in raw form on the CNTRICS Web site and are presently being prepared for publication.

The second Aim of the CNTRICS initiative is to develop a set of psychometric criteria and benchmarks for use in future norming studies of cognitive neuroscience tasks and imaging tools. This second meeting will also focus on how to develop versions of tasks that will measure specific cognitive processes of interest that are distinct from nonspecific or generalized deficits such as poor motivation, sedation, poor test-taking skills, and the like. Finally, during the meeting, strategies will be developed for optimizing the psychometric properties

of tasks prior to and during norming studies. All these principles will be applied within the constraints of the practicalities of administering tasks to schizophrenia patients in the context of a clinical trial (eg, duration of tasks, complexity of task instructions, ease of administration). Our hope is that this meeting will serve an educational purpose as well as identify the concrete characteristics and steps needed in order to help tasks from the cognitive neuroscience literature reach the psychometric standards necessary for use in clinical trials. The educational purpose is to inform basic cognitive neuroscientists as to the psychometric task properties that influence the utility of using their tasks and methods in clinical trial contexts because many basic scientists are unaware of the necessities and constraints of such study designs. This meeting, which will bring together psychometricians, clinical and basic cognitive neuroscientists, and scientists from industry, will be held in St Louis in September 2007.

The final aim of the CNTRICS initiative is to identify a set of cognitive tasks that measure the cognitive constructs identified in the first meeting that can be used to enhance translational research into impaired cognition in schizophrenia. We will again use an on-line survey process to develop a consensus on the criteria to use in identifying such tasks, which will include construct validity, the ability to provide a specific measurement of impairment in a specific cognitive mechanism in schizophrenia, suitability for incorporation into noninvasive imaging studies using methods such as fMRI or EEG/ERP's, and the existence of appropriate animal homologues. Notably, while evidence of good psychometric properties of such tasks will certainly be seen as a positive characteristic, existing evidence of good psychometric properties will not be a requirement for selecting tasks, lest we find ourselves in the same position as the initial MATRICS project. Instead, our goal will be to identify the most validated cognitive measures and to use future research to develop and establish appropriate psychometric (and practical) characteristics of such tasks, while retaining the initial validity that led to their selection in the first place. The final meeting will occur in Sacramento, California, in early 2008.

The CNTRICS initiative represents just one small step in the integration of modern technologies from cognitive neuroscience into the drug development process. As noted above, a necessary next step will involve norming studies to establish and optimize the measurement properties of the tasks developed in meeting 3. Similar studies will likely be needed for the brain-based measures using fMRI and other imaging approaches that can follow formal task development and optimization. Because the goal of this work is to have a positive impact on functional outcome, establishing links between these new measures and measures of functional disability will also need to be done.

In contrast to MATRICS, which focused on the needs of large-scale clinical trials and the later stages of drug development (phase 3), we believe that the initial products of CNTRICS will have their most immediate impact upon earlier phases of drug discovery and testing, such as initial human studies and proof of concept studies seeking very preliminary evidence of efficacy (phase 1 and 2 studies). In addition, the initial products of CNTRICS may also interact with initiatives designed to improve measurement in preclinical studies, by emphasizing and enhancing the development and use of validated homologous animal and human paradigms during the drug discovery processes. As the field matures, it is also possible that the same approach to measurement (either or both cognitive neuroscience-based behavioral paradigms or imaging paradigms) will be extended to the later stages of drug development.

Caveats

Although, we are highly optimistic that at enhanced focus on translational research will facilitate the process of drug discovery in schizophrenia, there are potential limitations or pitfalls to the approach outlined here. One major issue is that our understanding of the different types of molecular targets (and their interactions) that modulate cognition is in many ways still in a rudimentary stage, despite the many advances made over the past several decades. As such, the utility of using the tools of cognitive neuroscience to enhance drug discovery will by necessity reflect the dynamic interplay between basic knowledge development and application to clinical problems. A second related issue is the degree to which we have a good understanding of the psychological and neurobiological mechanisms behind the core cognitive deficits in schizophrenia. In particular, we should note that the cognitive domains being examined as part of the CNTRICS process do not include the construct of "processing speed." As recently noted by Dickinson and colleagues,[36] processing speed deficits may make an important contribution to impairments in a range of cognitive processes in schizophrenia. However, one of the challenges of examining processing speed in schizophrenia or in any other neurological condition is the construct validity of the measures. As noted by Dickinson, measures of processing speed such as Digit Symbol Coding tap many different processes, and it appears that more complex measures of processing speed elicit stronger effect sizes than less complex measures. As such, it is not yet clear how to assess general properties of the speed of cognitive processing in a manner independent of other fundamental components of processing, though recent modeling attempts are making progress on this front.[37–39] Second, the basic cognitive neuroscience literature does not yet point to a specific neural system or set of molecular targets that might be relevant to

understanding processing speed. There is emerging work suggesting that white matter integrity may be a critical component of processing speed,[40,41] and because research in this area proceeds, it may point to fruitful pathways for drug development in both human and animal models of processing speed.

Conclusion

The goal of CNTRICS is to enhance translational research. The application of cognitive neuroscience-based tools and measures in drug discovery is already underway in smaller scale projects. For example, a number of pharmaceutical companies have already begun to use the kind of cognitive tasks that are the focus of the present effort in behavioral studies as well as in studies using fMRI, in an effort to more effectively evaluate potential treatments for impaired cognition in schizophrenia. Similar approaches are also being taken in studies evaluating the effects of neurorehabilitation therapies. However, we believe that this translation process needs to be enhanced and facilitated so that it can be incorporated into a broader array of studies and contexts. By working toward developing a set of psychometrically robust, sensitive, and specific measures of cognition in schizophrenia, we hope to accelerate this process, so that in the very near future we will have effective therapies that will enhance the function and quality of life for people with schizophrenia.

Funding

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