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Harnessing cognitive neuroscience to develop new treatments for improving cognition in schizophrenia: CNTRICS selected cognitive paradigms for animal models

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Abstract

Over the past two decades, the awareness of the disabling and treatment-refractory effects of impaired cognition in schizophrenia has increased dramatically. In response to this still unmet need in the treatment of schizophrenia, the Cognitive Neuroscience Treatment Research to Improve Cognition in Schizophrenia (CNTRICS) initiative was developed. The goal of CNTRICS is to harness cognitive neuroscience to develop a brain-based set of tools for measuring cognition in schizophrenia and to test new treatments. CNTRICS meetings focused on development of tasks with cognitive construct validity for use in both human and animal model studies. This special issue presents papers discussing the cognitive testing paradigms selected by CNTRICS for animal model systems. These paradigms are designed to measure cognitive constructs within the domains of perception, attention, executive function, working memory, object/relational long-term memory, and social/affective processes.

Keywords

Psychosis; Psychopharmacology; Behavior; Rat; Mouse; Non-human primate

Over the past two decades, the awareness of the disabling and treatment-refractory effects of impaired cognition in schizophrenia has increased dramatically. Cognitive performance

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deficits in schizophrenia patients are strongly and consistently related to behavioral disorganization and poor functional outcome (Green et al., 2004; Harvey and Bowie, 2012; Kitchen et al., 2012). Along with this awareness has come an increasing emphasis on the importance of developing new treatments to alleviate these deficits. Toward this aim, the MATRICS meetings built a consensus between industry, academia, and the United States Federal Drug Administration (FDA) on how to move forward in the development of therapies for impaired cognition in schizophrenia (Marder et al., 2004). During this same period there has been an explosion of technical advances and new knowledge regarding the neural bases of cognitive processes on one hand, and risk factors in schizophrenia on the other (Insel, 2010). These advances have come in the fields of genetics and genomics, human neuroimaging and neurophysiology, and systems neuroscience. Converging data from animal and human research have resulted in a dramatic increase in knowledge regarding the neurobiological mechanisms underlying cognitive functions. Along with these advances has come a new set of behavioral and non-invasive imaging tools that enable us to measure the integrity of cognitive systems and assess the function of the neural systems that support cognition in human subjects, including those with schizophrenia and related disorders.

To capitalize on this knowledge, and to begin to develop a brain-based set of tools for measuring cognition in schizophrenia, cognitive neuroscientists and clinical researchers came together to initiate Cognitive Neuroscience Treatment Research to Improve Cognition in Schizophrenia (CNTRICS) (Carter and Barch, 2007) (http://cntrics.ucdavis.edu). The CNTRICS process has utilized meetings and surveys designed and organized by an executive committee (http://cntrics.ucdavis.edu/meetings.shtml) to bring together cognitive neuroscientists working in human and/or animal model systems, clinical researchers, systems neuroscientists with expertise in biomarker technologies, and preclinical translational behavioral neuroscientists. The inaugural aim, reflecting the cognitive neuroscience foundation of CNTRICS, was focused on enhancing the identification of cognitive `constructs' – definable cognitive processes that can be measured at the behavioral level and for which there exist clearly hypothesized and measureable neural-circuit mechanisms. Efforts toward this aim came to fruition with the first CNTRICS meeting (Washington, DC, 2007) in yielding a scheme of cognitive domains, and within each domain specific constructs considered to be most relevant to the cognitive impairments of schizophrenia (Carter et al., 2008). The next aims, addressed through two additional meetings, were to select and further develop cognitive neuroscience paradigms for use in humans that could selectively and parametrically measure these constructs at the behavioral level using tasks with a high degree of cognitive construct validity. Importantly, CNTRICS applied additional criteria to task selection, including the tasks' potential for exhibiting the parametric properties, reliability, exportability, and efficiency necessary for use in experimental medicine research and clinical trials (Barch et al., 2008, 2009c). CNTRICS participants selected tasks for measuring in human subjects specific constructs within the cognitive domains of Perception (Green et al., 2009), Attention (Nuechterlein et al., 2009), Executive Control (Barch et al., 2009b), Working Memory (Barch et al., 2009a), Long-term Memory (including object and relational memory) (Ragland et al., 2009), and Social and Emotional Processing (Carter et al., 2009). A table of the selected paradigms can be found at http://cntrics.ucdavis.edu/meetings.shtml (Materials for CNTRICS I: Third Meeting). In a second phase (CNTRICS II) we aimed to further develop homologous assays of the key cognitive constructs within biomarker studies (Carter et al., 2012) and animal model systems.

In this Special Issue, we report on the component of CNTRICS focused on the development of neurobehavioral assays of cognitive and social processes affected in schizophrenia to be applied in animal models. This initiative within CNTRICS was motivated by the observation

that efforts to find new treatments for improving cognition in schizophrenia have not yet delivered efficacious compounds. We identified as a major gap in these efforts the fact that many of the behavioral assays commonly used to characterize cognitive deficits in animal models have not been informed by recent advances in our knowledge about animal cognition and the neural mechanisms underlying specific cognitive processes. We also noted that most of these paradigms lacked adequate reliability, sensitivity and/or parametric properties necessary for detecting dose-dependent effects of drugs on cognitive abilities. We thus moved forward with the expectation that an iterative process integrating perspectives and expertise across investigators working in human and animal cognition would be necessary to fill this gap.

With the goal of improving integration and flow across preclinical studies and early phase human studies, we organized two CNTRICS meetings that brought together a broad range of researchers from both industry and academia with expertise in the use of animal models to elucidate cognitive processes relevant to schizophrenia (http://cntrics.ucdavis.edu/meetings.shtml). The first of these meetings (CNTRICS II: Developing Homologous Animal Models, St. Louis, April 2010) was focused on clarifying which CNTRICS constructs could be validly targeted for measurement in animal models. This meeting included extensive discussions on the criteria to be used to evaluate homology, at both the psychological and neural-substrate levels, between animal and human cognition. Specifically, we focused on issue of construct validity at two levels by addressing evidence that (1) the behavioral paradigm isolates the cognitive construct (i.e. from alternate mechanisms that might drive the behavior) by selectively varying task demands thought to tap specifically into the construct of interest and (2) the targeted cognitive process (and its behavioral manifestation) is mediated by homologous neural circuits in human subjects and animal models. In the second meeting (CNTRICS II: Selecting Translational Animal Model Paradigms, Washington, DC, April 2011), we recommended for further development a set of animal cognitive testing paradigms that measure function within each of the CNTRICS constructs of interest. Like CNTRICS I meetings, this meeting was preceded by a survey sent to a broad range of investigators in the field from both industry and academia. This survey solicited ideas on specific paradigms, new or existing, that could be used to measure the CNTRICS constructs of interest and for screening of potential treatment effects on cognition.

The articles in this Special Issue report on discussions of the constructs and animal cognitive testing paradigms considered and selected in CNTRICS meetings. We focused on the cognitive constructs selected in CNTRICS I for which homologous constructs could be measured in rodents and non-human primates. Table 1 summarizes the cognitive domains, constructs within each domain, and the cognitive testing paradigms selected for further development and implementation in animal models. Each paper in this issue covers one cognitive domain; each outlines the key issues relevant to using animal behavioral paradigms to study the constructs of interest, provides a summary of the paradigms considered, and then reviews each of the selected paradigms. For each of the selected behavioral testing paradigms experts in the field discuss key structural elements of the paradigm, the known or hypothesized neural substrates and pharmacology of performance in the task, and challenges in task implantation. In addition to these `constructs and paradigms' papers, we include a paper on the consideration of species differences in designing and interpreting behavior in such paradigms.

Throughout the CNTRICS II process, the primary criterion for task selection and development has been *construct validity*. In cognitive neuroscience, this form of validity is established by showing that performance in the task varies selectively as a function of demands on the targeted construct and is mediated by homologous neural circuit

mechanisms in humans and the animal model species. The primacy of construct validity recognizes that *predictive validity* – that is, the ability of the paradigm to predict the efficacy of treatment or other manipulations to alter a specific cognitive function in schizophrenia patients – is the ultimate goal of translational research; and that predictive validity is a function of construct validity. To put this in concrete terms: (1) cognitive processes and the behaviors reflecting those processes are mediated by activity within specific neural circuits and (2) drugs act the biological level – to change neural circuit function. Thus, finding new cellular and molecular targets for treatments aimed at improving cognition in schizophrenia requires us to apply to our animal models cognitive paradigms that assay the function of neural circuits homologous with those hypothesized to mediate the cognitive construct of interest in humans. This approach also facilitates consideration of neurocognitive processes in the development of non-pharmacological treatment strategies.

Genetic and neurobiological disease models play an important and complementary role in this process. We introduce the term `animal modelers' here to refer collectively to researchers using genetic, neurodevelopmental, pharmacological, and behavioral manipulations in animals to study one or more putative pathogenic processes in schizophrenia. Animal modelers include geneticists studying mouse models that recapitulate or inform on risk genes, researchers developing models of perinatal risk factors, and cognitive and behavioral neuroscientists using manipulations that examine potential causal or mediating relationships connecting neuropathology, imaging or electrophysiological neuropheno-types, cognition, and behavior. Given the necessary breadth of research objectives embedded within the overall goal of using animal models to increase our understanding of schizophrenia, it is a challenge to maintain construct validity in the behavioral paradigms used to characterize these disease models. However, meeting this challenge is critically important for understanding the neurobiology of cognitive deficits in schizophrenia and for predicting the efficacy of putative pharmacotherapy. Specifically, the argument for these requirements is as follows: (1) schizophrenia is defined *behaviorally*, in large part by disruption of cognition and (2) most potential biomarkers of schizophrenia are proxies of neural circuit activity. Thus, neural circuit assays (which include behavioral tasks known to recruit and depend on specific circuits) are the ultimate assays for understanding the multitude of genetic and molecular mechanisms associated with the risk for schizophrenia, and for testing novel pharmacological treatments for cognitive enhancement. In addition, task properties such as reliability (in particular test–retest reliability for within-subjects measurement of drug effects), sensitivity to potential drug effects, and efficiency are critical to the success of these paradigms. Indeed, discussions at both CNTRICS Animal Models meetings recognized and prioritized these components of paradigm development. Nonetheless, it was also emphasized that these properties could not be achieved at the expense of cognitive and neurobiological construct validity.

The CNTRICS process, including this Special Issue, is not meant to be prescriptive or exclusive. Nearly 25 million people in the world suffer from schizophrenia or a related disorder. Moreover, schizophrenia-associated cognitive impairment accounts for a large proportion of the worldwide humanistic burden of the disorder (Kitchen et al., 2012), in part due to the lack of effective pharmacotherapy (Harvey and Bowie, 2012). So it should go without saying that we need multiple efforts at improving treatment discovery, with multiple perspectives. The CNTRICS process was informed by preceding innovative and well-developed translational cognitive testing systems (Geyer, 2008; Keeler and Robbins, 2011) and there has been considerable cross-fertilization across these initiatives. Further, we hope that one ramification of cognitive neuroscience-based efforts, including CNTRICS, would be greater reliance on cognitive and neurobiological construct validity in preclinical schizophrenia research. This sentiment applies to research in animal model systems designed to recapitulate a genetic or pathophysiological mechanism in schizophrenia

(`disease models'), as well as to animal experiments designed to understand pharmacological modulation of a specific cognitive process affected in the disease. Whether researchers apply the paradigms selected in the CNTRICS process, adapt a paradigm that they already find useful, or develop new paradigms (e.g. Mar et al., 2013; Oomen et al., 2013; Simpson et al., 2012), the necessary steps in paradigm selection should be to harness the rich literature in experimental psychology and cognitive neuroscience to define and measure the cognitive process(es) of interest and their neural mechanisms. If these steps are more routinely applied to the selection of behavioral testing paradigms used in animal disease models and psychopharmacological studies, much progress will have been made.

In summary, it is widely agreed that bringing together researchers with different theoretical perspectives, technical expertise and empirical knowledge to solve a problem such as cognitive enhancement in schizophrenia is a good thing. The insight of CNTRICS and like-minded initiatives is that requiring those researchers to ground their discussions and experimental designs in construct validity assures translation in the most literal sense. It assures that the all researchers will define the cognitive processes to be examined (and improved) in humans, in part as a function of the paradigms used to measure them, and that translation will be achieved by maintaining construct validity across the human and non-human paradigms targeting a given cognitive process. The `construct validity requirement' requires us to move from comparing measurements at a nominal or categorical level to testing parametrically whether a human and animal model paradigm are testing the same process at both the behavioral and neural circuit level. We hope this approach will improve the efficacy of the translational research process and ultimately lead to new effective strategies for improving cognition in those suffering from schizophrenia and related disorders.

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Abbreviation

CNTRICS	Cognitive Neuroscience Treatment Research to Improve Cognition in Schizophrenia.

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Table 1

CNTRICS constructs of interest and selected paradigms for animal model systems.

Construct	Selected paradigms
Perceptual processes	
Gain control: The processes whereby neuronal responses adapt and animals adjust behavior to take into account an immediate perceptual context, done in order to optimize use of a limited dynamic signaling range.	*Prepulse inhibition of the startle reflex:* Attenuation of a startle response as a function of immediate pre-exposure to a sub-threshold stimulus. *Mismatch negativity and related tasks (`odd ball' or frequency-variation paradigm):* Neural and behavioral responses to a change in stimulus characteristics.
Integration: The processes linking the output of neurons that typically encode local attributes of a scene into a global complex structure, more suitable to the guidance of behavior.	*Coherent motion detection:* Animals (or neurons) respond when coherent motion of multiple parts (usually points or line segments) is detected. *Contour detection*: Animals (or neurons) respond when elements form a contour (the outcome measure for these tasks is threshold).
Attention	
Control of attention: The ability to guide and/or change the focus of attention in response to internal representations (and prevent interference of this process by external noise).	*Distractor sustained attention task:* Animal is required to "report" (with two different responses) whether or not a signal occurred. Salience and probability of the signal, and salience of noise (non-relevant stimuli), are varied. *5-Choice serial reaction time and continuous performance tasks:*Animal is required to detect brief stimuli presented at one of 5 possible locations. Detection is typically reported with a nose poke or touch on screen. Trials occur continuously in rapid succession. Non-signal trials reported by withholding responses can be added. Attentional load is varied with (1) size of the attentional field, (2) interference level, and (3) probability of stimuli at specific locations.
Executive function	
Rule generation and selection: The processes involved in activating task-related goals or rules based on endogenous or exogenous cues, actively representing them in accessible form, and maintaining and using this information to bias attention and response selection during the interval needed to perform the task.	*Set-shifting task (`intra-dimensional/extra-dimensional shift' task):* Following acquisition of a compound stimuli on the basis of one dimension (while properties within the other dimensions are varied randomly), the rule is shifted such that a previously irrelevant dimension (i.e. `set') becomes relevant. *Reversal learning (including probabilistic, 3-choice, and serial reversal):* The contingencies of a discrimination rule are reversed: the stimulus previously associated with the reward is now associated with non-reward and vice versa.
Dynamic adjustments of control: The processes involved in detecting recent conflict or errors in ongoing processing and making rapid (within or inter-trial) adjustments in control of performance.	*Stop-signal task (assessment of post-error slowing):* The animal is required to use an external stimulus to cue the interruption of a prepotent, already-initiated motor response.
Working memory	
Goal maintenance: The processes involved in maintaining information about task-related stimuli, goals and rules and using this information to bias attention and optimize response selection during task performance.	*Delayed matching/non-matching tasks:* This includes operant-box and maze versions by which animal is required to make a choice that matches or does not match a choice made on a previous trial. The time between trials and number of past choices required to remember are varied.
Working memory capacity: The size of the array of items or events that can be held online while the animal uses that array to make choices.	*Stimulus (usually odor)-span task:* An extension of the delay non-match-to-sample in which an additional stimulus is added with each trial and the animal is required to identify the stimulus not previously sampled.
Interference control: The ability to hold required information over time in the face of competing, irrelevant information or intervening events.	*N-back tasks:* Stimuli are presented serially and continuously. Animal tracks a target stimulus but must wait until when cued to respond. Upon cue stimulus, the animal responds if target had been presented since previous cue. Memory load is a function of number of stimuli intervening between target and cue.
Motivation and reinforcement learning	
Reinforcement learning: Acquisition of an instrumental response in order to gain access to an appetitive (positive reinforcement) outcome or avoid an aversive outcome (negative reinforcement). Positive reinforcement was considered the process of greatest relevance to avolition in schizophrenia.	*Probabilistic reinforcement learning:* Acquisition and adjustment of an instrumental response according to probability of the reinforcer. *Response-biased probabilistic reward learning:* The effect of differential reinforcement probability of two difficult-to-discriminate stimuli on response bias. *Pavlovian autoshaping:* Pavlovian appetitive conditioning to a cue in the context of an instrumental response that does not depend on the cue.

Construct	Selected paradigms
Motivation: The valuation of an outcome (the conditioned stimulus or reinforcer) and expending work or guiding behavior on the basis of the value or probability of that outcome.	*Effort-related tasks (e.g. Progressive Ratio):* Progressively or randomly increasing the effort requirement (response ratio, height of barrier, duration of responding) for earning reward. *Outcome devaluation and contingency degradation task:* Assessing impact of reward devaluation (through saturation or negative association) on positively-reinforced responding.
Object/relational long-term memory	
Relational encoding and retrieval: The processes involved in memory for stimuli/elements and their associations with coincident contexts, events or outcomes.	*Paired associate learning:* Animal is required to encode and retrieve object-location associations as a function the pairing of two objects (drawn from a larger set). *Object in place scene learning:* A variant of conditional discrimination requiring the animal to use a complex visual background (or context) to guide a choice between one of two possible cued responses (cues are presented in foreground).
Social/emotional processing	
Socioaffective recognition: The ability to detect, recognize social cues emitted from a conspecific and respond appropriately.	*Social recognition/preference:* Variants include comparing responses to novel versus familiar social objects, or social objects versus neutral or non-living objects. Outcome measures include approach, exploration time, species-appropriate social behavior. *Emotional and intention recognition using visual scan of social scenes:* Animals (usually non-human primates) are shown video/audio presentation of social signals from conspecifics (e.g. facial expressions, body movements, vocalizations). The task can require the animal to discriminate between affective states or individual conspecifics. In addition to the operant response (a saccade), gaze pattern/speed, reaction time to emotional versus non-emotional stimuli, and autonomic responses are measured.