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CNTRICS Imaging Biomarkers Selection: Working Memory

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The sixth meeting of the Cognitive Neuroscience Treatment Research to Improve Cognition in Schizophrenia (CNTRICS) consortium was focused on selecting promising imaging biomarker measures for each of the cognitive constructs selected in the first CNTRICS meeting. In the domain of working memory (WM), the 2 constructs of interest were "goal maintenance" and "interference control." CNTRICS received 7 task nominations for goal maintenance and 3 task nominations for interference control. For goal maintenance, the breakout group for WM recommended the AX Continuous Performance Test/Dot Pattern Expectancy (DPX) and the Switching Stroop task for translation and further development for use in clinical trial contexts in schizophrenia research. Notably, these same 2 paradigms were recommended for "rule generation and selection" in executive control, a highly related construct. For interference control, the breakout group recommended the Suppress Task and the Sternberg Item Recognition Paradigm for translation for use in clinical trials. This manuscript describes the ways in which each of these tasks met the criteria used by the breakout group to recommend tasks for further development. In addition, the group revisited the construct of WM capacity. Since the initial CNTRICS meeting, a growing body of work has emerged on the neurobiological substrates of WM capacity, making measure of this construct ready for translation. The group suggested a promising imaging biomarker measure for capacity, a version of the change detection task that measures delay activity over posterior parietal and occipital cortex.

Key words: schizophrenia/treatment/working memory/prefrontal cortex/capacity

CNTRICS Final Task Selection: Working Memory

Working memory (WM) continues to be one of the most well-studied cognitive domains in schizophrenia.[1] There is a rich body of work examining both the psychological and neurobiological mechanisms that play a role in WM,[2] with a general consensus that there are a number of different subcomponents of this construct that may have dissociable neural mechanisms.[3,4] A common definition of WM is that it refers to the maintenance and manipulation of information over a short period of time (up to ~30 seconds). This maintained information can be either specific stimuli or task goals used to guide the current action plan, and the contents of WM can be protected from interference due to either distracting information or decay over time.

A detailed review of the different models of WM is beyond the scope of this review. However, there are 2 prominent models of WM. Baddeley's model[3] proposes 4 major components of WM; (1) the visuospatial scratch pad, a short-term storage buffer for visual information; (2) the phonological loop, a short-term storage buffer for verbal information; (3) a central executive that supports the manipulation and transformation of information held within the storage buffers; and (4) an episodic buffer, in which complex multimodal events are integrated and stored on line.[3] In contrast, Cowan's model postulates that the information represented in WM is an activated portion of long-term memory that is currently in the focus of attention[4] and does not argue for structural or neurobiological differences in the representations involved in WM vs episodic memory. The central executive has been associated with the function of dorsolateral prefrontal cortex (DLPFC) in many studies, while the storage buffers have been associated with both inferior frontal and posterior parietal function.[5] Furthermore, a number of different neurotransmitter systems are thought to play differential roles in WM, including glutamate, dopamine, Gamma Amino Butyric Acid (GABA), and norepinephrine.

There have been numerous demonstrations that individuals with schizophrenia exhibit deficits on a wide range of WM tasks and that these deficits are associated with impairments in the function of neural circuits that support WM function.[1,6] Given the body of work on WM in schizophrenia, Cognitive Neuroscience Treatment Research to Improve Cognition in Schizophrenia (CNTRICS) initially identified measures of 2 aspects of WM as ready for immediate translation for development and use in clinical trials in schizophrenia: (1) goal maintenance and (2) interference control. Goal maintenance was defined as: "The processes involved in activating task-related goals or rules based on endogenous or exogenous cues, actively representing them in a highly accessible form, and maintaining this information over an interval during which that information is needed to bias and constrain attention and response selection." Interference control was defined as: "The processes involved in protecting the contents of WM from interference from either other competing internal representations or external stimuli."

As discussed in detail in the manuscript describing the very first CNTRICS meeting that involved the selection of WM constructs, there were several reasons for the focus on the constructs of goal maintenance and interference control, including evidence for the cognitive and neural validity of these constructs, as well as the work in schizophrenia pointing to deficits in these components of WM, in contrast to less evidence for impairment in components such as simple maintenance (see ref.[7] for a more detailed review). There are numerous studies identifying deficits in goal maintenance in schizophrenia, eg.[8] These deficits have frequently been associated with alterations in the function of the DLPFC and parietal cortex, eg,[9] and with impairments in both the dopamine and GABA systems.[10] There is also data suggesting that interference control in WM maintenance is impaired in schizophrenia, eg,[11] though it is not clear whether the neural correlates of such impairments are different than those associated with goal maintenance.

As described in the other articles in this special issue, the goal of the sixth CNTRICS meeting was to solicit and evaluate nominations for promising paradigms that could serve as imaging biomarkers of each of these 2 constructs. The nominators were asked to provide a description of the task and to provide information on 6 domains relevant to selecting the most promising tasks: (1) cognitive construct validity, (2) neural construct validity, (3) psychometric characteristics, (4) results in schizophrenia, (5) evidence of pharmacological sensitivity, and (6) the availability of animal models. The overview article of this special section outlines why these criteria were selected and applied during the group discussions. Here, we briefly review the ways in which each of these tasks met the criteria used for selection.

Goal Maintenance

CNTRICS received 7 initial nominations for the goal maintenance component of WM: (1) the AX Continuous Performance Test (AX-CPT)/Dot Pattern Expectancy task (DPX) with functional magnetic resonance imaging (fMRI), (2) Switching Stroop Task with fMRI or event-related potential (ERPs), (3) the Sternberg Item Recognition Paradigm with fMRI, (4) spatial delayed response task with fMRI, (5) the NBack task with fMRI, (6) the P300 oddball task with ERPs, and (7) the Tower of London planning task. The AX-CPT/DPX task had been selected as a recommended behavioral measure of goal maintenance in the third CNTRICS meeting and recommended for further development. Notably, both the AX-CPT/DPX and the Switching Stroop had also been nominated as measure of rule generation and selection (an executive function construct) for the current meeting.

Task Recommended as Measures of Goal Maintenance

After much discussion in the WM breakout group, it was decided that we would also select the AX-CPT/DPX and the Switching Stroop as the most promising imaging biomarker measures for goal maintenance as there is a great deal of overlap in the constructs of goal maintenance and rule generation and selection, which is not surprising given the intimate connections between the psychological and neurobiological mechanisms supporting specific aspects of WM and executive control. Briefly, the reasons for selecting these paradigms included evidence for their construct validity, evidence that the paradigms tap the neural systems thought to be relevant for these constructs (including DLPFC), evidence that performance and brain activation are modifiable by either pharmacological or psychological means, evidence for a parallel animal version (at least for the AX-CPT/DPX), and initial evidence for good psychometric properties (at least for the AX-CPT/DPX). The reader is referred to the executive control article in this special issue for a more detailed review of these tasks and the rationale for their application in imaging biomarker studies of this domain in schizophrenia.

Other Tasks Considered As Measures of Goal Maintenance

There were 3 imaging biomarker paradigms that the breakout group members felt were good measures of the maintenance and updating of specific items in WM but not necessarily of goal maintenance per se. The first of these was the Sternberg Item Recognition Paradigm (SIRP). This paradigm involves the presentation of a memory set (letters, digits, objects, words, etc.) to participants, with a variable number of items to be memorized per trial (called the "set size"), eg.[12] Participants are then presented with probes after a delay and asked to indicate whether the probe item was in the memory set. This paradigm is a good measure of the ability to maintain and search items in WM, and it has been used extensively in schizophrenia.[13] Versions of this paradigm used with fMRI robustly activate brain regions thought to be involved in WM storage (such as inferior

frontal cortex and posterior parietal cortex) and can also activate DLPFC at higher load levels.[13] However, the design of the paradigm does not offer a way to focus specifically on measures of goal maintenance as opposed to maintenance of items. The group did feel that the SIRP could be promising as a measure of interference control in WM, as described below.

The second measure of item maintenance nominated was the spatial delayed response task. This task involves the presentation of one or more spatial locations, with a requirement to indicate memory for the location(s) after a delay, eg.[14] This paradigm has been used extensively to study spatial WM in nonhuman primates and humans and shown to recruit the DLPFC, eg.[14] It has also been used in both behavioral and fMRI studies of WM in schizophrenia, eg.[1,15] It was felt that this task is a valid and reliable measure of the maintenance of spatial information but does not offer a way to isolate goal maintenance.

The third measure of item maintenance nominated was the NBack task. This is a continuous performance task in which participants are presented with a series of items and asked to respond in a way that varies the number of items that need to be held in WM. In many ways, the NBack task is a canonical imaging biomarker of WM in general because it robustly activates all of the brain systems thought to be involved in WM and reliability elicits impairments in WM performance and brain activation in schizophrenia, eg.[16] However, it's strengths as a potent recruiter of multiple WM brain systems and a task with high sensitivity to disease likely derive from the fact that it conflates many different components of WM, including goal maintenance, item maintenance, protection from interference, updating, etc. Thus, it is not particularly useful as a selective measure of goal maintenance, though it may have good utility in other contexts.

The Tower of London Planning was also nominated. This task requires participants to determine how to rearrange a series of balls on sticks or in pockets in order to match a template. It does activate frontal-striatal circuitry thought to support goal maintenance in WM, and individuals with schizophrenia are impaired on this task.[17] However, like the NBack, it conflates many different components of WM, including goal maintenance, item maintenance, protection from interference, updating, etc.

The P300 Oddball paradigm was also nominated as a measure of goal maintenance. In a typical paradigm, participants hear a sequence of low- and high-pitched tones, with one of these occurring frequently (eg, 90%) and the other occurring infrequently (eg, 10%). Participants can respond by either pressing a button when they detect the infrequent pitch or by counting the occurrences of the infrequent pitch. The P300 is an ERP component that can be measured from the waveform elicited by the infrequent pitch or from the infrequent minus frequent difference wave. The magnitude and latency of the P300 are sensitive to a variety of factors related to attention and WM, and the P300 is robustly reduced in schizophrenia.[18] However, the breakout group felt that it was a not a specific measure of the neural systems involved in goal maintenance in WM.

Interference Control

CNTRICS received 2 nominations for the interference control in WM construct: (1) the Suppress Task and (2) the Sternberg Item Recognition Paradigm. The group felt that the both tasks should be recommended for translation as measures of interference control in WM. A variant of the Suppress Task (Ignore-Suppress) was nominated as a behavioral measure in the third CNTRICS meeting, as well as a variant called the Recent Probes Task, which is similar to the "suppress" component of the Ignore-Suppress Task. At that time, only the Recent Probes task was recommendation for translation because the Ignore-Suppress Task was newly developed and had little evidence to support it use. However, more information is now available, particularly in terms of the utility of the Suppress component as a measure of interference control, as described below. The Operation/Symmetry Span task was also recommended for translation as a behavioral measure in the third CNTRICS meeting. It continues to be a good behavioral measure of interference control but has not been used extensively as an imaging biomarker.

Suppress Task

Background and Description of the Task. The Suppress Task is a variant of the Sternberg Item Recognition Paradigm.[12] Several variants of the Suppress Task have been tested that differ with regard to how the active and irrelevant sets are cued. As shown in figure 1, in the most widely studied variant, the encoding display consists of items presented in 2 colors (eg, half in blue, half in red, or any other color combination). After the encoding display goes off the screen, a cue is presented to denote that items presented in one color are the relevant set (eg, red items), and the words in the other color are the irrelevant set (eg, blue items), eg.[19,20] For example, a red color patch may indicate to the participant that they should retain items that had been printed in red and discard from memory items that had been printed in blue. After the cue, the participants retain a relevant set in memory and respond to recognition probes. There are 3 types of recognition probes, "positive," "negative," and "lure." "Positive probes" match an item in the relevant set and thus require a positive response. "Negative probes" were not presented on the trial and thus require a negative response. Notably, care is often taken to ensure that negative probes had not been presented for several trials so as to serve as a low-familiarity control. "Lure probes" match an item in the irrelevant set and

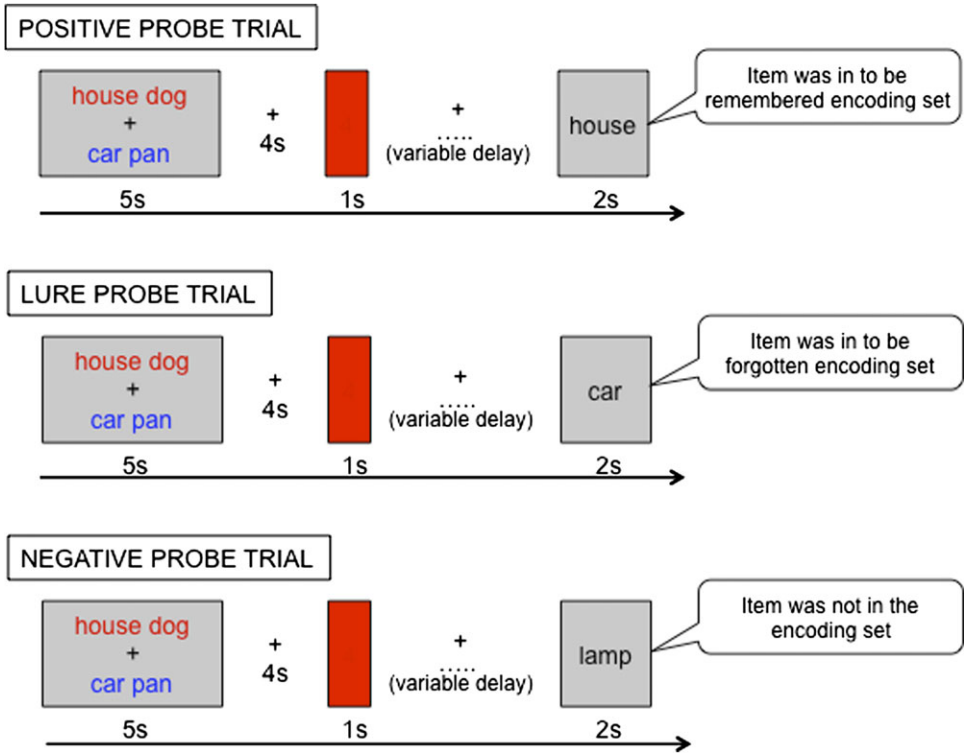

Fig. 1. Example schematic of the Suppress Task. The 3 different trial types are illustrated. In positive probe trials, the probe item was in the part of the encoding set that was cued to be remembered and the correct response is "target." In lure trials, the probe item was in the part of the encoding set that was cued to be forgotten and the correct response is "nontarget." In negative probe trials, the probe item was not in the encoding set and the correct response is "nontarget."

also require a negative response. Behaviorally, responses to lure probes demonstrate increased reaction times (RTs) and error rates (ERs) relative to responses to negative probes (intrusion cost). These intrusion costs have been attributed to the high familiarity of lure probes inducing proactive interference.[21] Two phases of the Suppress Task have been examined in order to measure interference control in WM. The first phase involves investigating processes involved in the selection of the relevant set/discarding of the irrelevant set in response to the cue. We refer to this as the "cue phase." The second phase involves investigating processes involved during retrieval in response to the probe. We refer to this as the "probe phase."

Construct Validity and Neural Systems. Several studies have used event-related fMRI designs to examine activations during the probe phase, eg.[19,20,22] In this phase, the critical contrast of interest is between activations to lure probes compared with activation to negative probes. Lure probes have consistently demonstrated increased activation in left lateral prefrontal cortex (LPFC) relative to negative probes. Left LPFC is considered to be a critical locus of interference control of WM.[21] In 2 studies, this activation difference has correlated with RT differences,[19,20] although the sign of the correlation has been inconsistent. These discrepancies may be due to differences in the way the data were modeled to either isolate probe phase activations independent of the cue phase or not. Functional connectivity analysis demonstrates that left LPFC functional interacts with the medial temporal lobe when resolving interference from lure probes relative to negative probes.[23] These data are consistent with models that propose the left LPFC is involved in the selection of contextual details to resolve proactive interference.[21]

There are 2 published reports that have examined activations during the cue phase.[20,24] In both, cue phase activations were examined by manipulating the difficulty of selection. These studies compared remember cues that cued the relevant set (compatible cue) or forget cues that cued the irrelevant set (incompatible cue). In both reports, forget cues produced heightened activation relative to remember cues in left LPFC, as well as in the anterior cingulate cortex (ACC) and intraparietal sulcus (IPS). Nee and Jonides[20] measured the duration of the selection process and found that activations in left LPFC, ACC, and IPS correlated with parametric increases in RT, confirming the association between the selection process and neural activations.

Published reports have either examined the cue phase or the probe phase, but not both. However, we believe it is of interest to examine both phases within a single design. First, it is clear that both phases provide useful and

robust data. Second, examining both phases affords the ability to dissociate "proactive" components of control associated with the cue phase from "reactive" components of control associated with the probe phase.[25] As we detail further below, preliminary evidence suggests reduced proactive control during the cue phase in patients with schizophrenia relative to healthy controls and increased reactive control during the probe phase. Hence, designs that afford examinations of both cue and probe phases appear to be feasible and instructive. Therefore, we recommend separating the cue and probe phases by at least 4 seconds in order to dissociate blood oxygen level dependent responses to each event. It may be desirable to increase this interval further to examine maintenance processes. In this way, the effect of simple WM load can also be examined (ie, precue maintenance-postcue maintenance). This contrast can then be used to dissociate executive effects from those of simple storage.

Results in Schizophrenia. Smith and colleagues[26] examined the performance of patients with schizophrenia and matched controls in the Suppress Task and found that patients demonstrated increased intrusion costs. By contrast, performance in the Ignore Task, an analogue of the Suppress Task that examines interference control in perception, did not differentiate patients and controls. Hence, patients appeared to have a selective impairment in interference control in WM. Preliminary unpublished fMRI data indicate that patients with schizophrenia show reduced activation in the cue phase of the Suppress Task. By contrast, patients show increased activation during the probe phase relative to healthy controls. Collectively, these data indicate that the Suppress Task can identify impairments in the neural systems associated with interference control in WM in schizophrenia.

Pharmacology and Animal Models. The Suppress Task has not been studied with pharmacological manipulations in humans. Animal paradigms that recruit overlapping processes (eg, set formation and inhibiting attention to irrelevant stimuli) have been used to dissect neural substrates and pharmacological modulation.[27] However, the equivalent of the Suppress Task has not yet been applied to animal models. Such a task could be developed as a variant of stimulus set learning paradigms. As a potential point of translation, we are aware of a single published report of the Suppress Task using nonverbal material.[28] This study examined the probe phase and reported greater activation for lure probes relative to negative probes in the superior parietal lobule and precentral sulcus. However, comparisons were restricted to regions of interest sensitive to spatial WM, and it was unclear whether left LPFC demonstrated differential activation.

Measurement Properties. Nee and colleagues have calculated split-half reliabilities of the intrusion cost in the Suppress Task in 2 different experiments. In the first, the split-half reliability was quite high (0.87), and in the second, it was substantially lower (0.32). In the latter experiment, the Suppress Task was combined with a stop-signal task to compare interference control processes in WM and responses,[29] which may have made the task somewhat more volatile. More data are needed on the reliability of the imaging results.

Future Directions. Further development of the Suppress Task will require additional neural data in patient populations and psychometric work examining the optimal length of the task and test-retest reliability for both the behavioral and neural data. At the present time, there is only a one published report of neural activations in psychiatric patients (major depression).[30] The fact that individuals with schizophrenia demonstrate increased intrusion costs behaviorally relative to healthy controls suggests that neural differences are likely to be found in left LPFC. As noted above, to assure translation across human and animal paradigms, nonverbal forms of the task will be needed. Understanding deficits in the Suppress Task will also be fostered by further elucidation of the mechanistic underpinnings of the Suppress Task. Whereas retrieval processes elicited during the probe phase are fairly well characterized, the processes that rid irrelevant content from WM are somewhat less clear. Some of the evidence suggests that time spent rehearsing the relevant set and the size of the relevant set relative to the irrelevant set may be factors that affect intrusion costs. These factors are likely to influence the degree to which representations in the relevant and irrelevant sets compete. It is possible that the relevant and irrelevant sets have mutually inhibitory competitive interactions such that strengthening the relevant set may serve to dampen the irrelevant set. Such competitive dynamics have been proposed in other memory paradigms and systematic investigations of these mechanisms would serve to illuminate our understanding of interference control in the Suppress Task, how these mechanisms may go awry in schizophrenia, and how they may be modified by psychological or pharmacological means.

The Sternberg Item Recognition Paradigm

Background and Paradigm Description. Another variant of the Sternberg Item Recognition Paradigm (SIRP)[13] has been used extensively in studies of schizophrenia (see figure 2 for an illustration). Its original design was as a general measure of WM in schizophrenia, but it can be adapted for use as a specific measure of interference control by modulating the distractibility of the probe items. To perform the SIRP, participants must maintain a set of targets (in this case, digits) in WM. They are then presented with a series of probe digits and respond by indicating whether the probe is a target

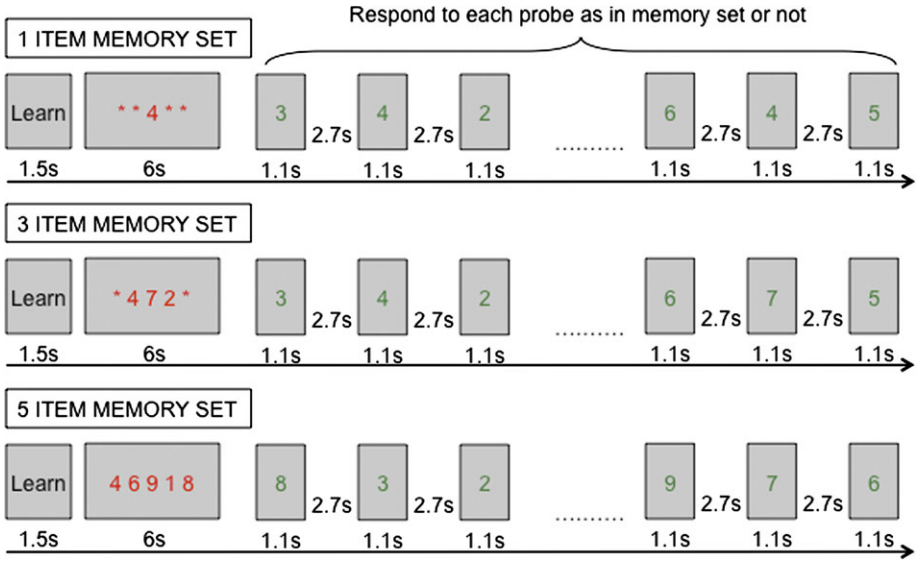

Fig. 2. Example schematic of a variant of the Sternberg Item Recognition Paradigm frequently used in functional MRI studies of individuals with schizophrenia. Three different memory load trial types are illustrated. In this variant, 14 probes are presented in each block, with 7 of the probes being items that were in the memory set (targets), and 7 being items that were not in the memory set (foils).[31]

(a member of the WM set) or a foil (not a member). There is a linear relationship between set size (the number of targets) and RT, the time needed to indicate whether a presented digit is a target or a foil.[12] When RTs are plotted against set size, the "slope" of the linear function indexes the speed of mentally scanning the contents of WM (ie, the increment in RT for each additional target). The "intercept" provides a measure of the motor, perceptual, and cognitive functions (eg, response selection) that do not vary as a function of set size. This property of the SIRP allows WM and non-WM components of RT to be dissociated, which is particularly useful in patients with motor slowing. Similarly, fMRI activation in the WM network, including the DLPFC, increases as a function of set size.[13] It is important to note that linear relations are observed only up to the point where WM capacity is not exceeded (ie, performance is still relatively error-free). When WM capacity is exceeded, RTs become erratic and DLPFC activation may decrease, possibly reflecting the use of strategies not involving WM, including guessing. Studies of schizophrenia have generally stayed within WM capacity using set sizes of 1, 3, and 5 target digits. In 2 large-scale multisite studies involving hundreds of patients with schizophrenia and demographically matched healthy controls, even though patients made significantly more errors than controls, their mean accuracy exceeded 90% at a WM load of 5 target digits,[31,32] though this does not necessarily rule out a potential influence of differential group performance on level and nature of activation differences between individuals with schizophrenia and controls. Nonetheless, the fact that individuals with schizophrenia perform very well on this task may make it either less susceptible to this potential confound than tasks that elicit extremely impaired performance among patients or easier to explicitly examine performance related confounds by focusing only on correct trials or by examining subgroups matched on task performance.

Construct Validity Neural Systems. In the fixed set version of the SIRP (see figure 2), there is one memory set followed by multiple probes that are presented in a rapid succession. Accurate responding is predicated on the maintenance of digits in WM for the duration of the probe epoch in the face of interference from nontarget probe digits (ie, foils) that serve as distractors. While other areas of the cortex, particularly extrastriate visual areas, are capable of sustaining a response to a brief stimulus for periods up to several seconds, the ability to support sustained activity in the face of interference is thought to be one of the distinguishing characteristics of the DLPFC.[14] Fixed set versions of the SIRP reliably give rise to activation in a network of regions including the DLPFC, IPS, lateral premotor cortex, supplementary motor area, and the insula that has been associated with WM performance on a range of tasks.[5] The SIRP can also demonstrate activation in left IFC region thought to be specifically associated with interference control, and this activity can be isolated by versions of the paradigm that enhance probe interference.

Results in Schizophrenia. fMRI studies of WM have demonstrated both hypoactivation and hyperactivation of the DLPFC in schizophrenia,[9,13] which are both thought to reflect "inefficient" prefrontal cortex function, eg.[33] On the SIRP, with a WM load of 5 digits, patients show increased DLFPC activation, which can be considered inefficient because given identical WM demands, and patients require greater DLPFC recruitment to achieve

a lower level of performance (ie, slower, less accurate) than controls, eg.[31] That DLPFC recruitment in patients is inversely related to ER suggests that the increased activation is necessary for accurate task performance. When WM capacity on the SIRP is exceeded (eg, with 7 or 9 target consonants) and performance decreases, patients show DLPFC hypoactivity relative to controls, eg.[34] These findings are consistent with the "inverted-U" shaped neurophysiological response of the DLPFC to increases in WM load observed in healthy individuals. DLPFC recruitment increased with greater WM load until capacity was reached, at which point DLPFC activation decreased. This inverted-U shaped function is shifted to the left in patients (ie, peaks at a lower WM load), reflecting reduced WM capacity.[33]

Pharmacology and Animal Models. To date, the SIRP has not been studied with pharmacological manipulations. There is no animal model of the type of SIRP typically administered in humans, although there are related task variants of object and spatial memory that have been used in monkeys.[35] Paradigms requiring item recognition are extensively used in rodents. However, common forms are designed to isolate object encoding and recognition rather than retrieval of set information. They also largely rely on unconditioned responses (eg, approach) to the probe as a proxy of recognition. As such, these forms capture processes mediated by the medial temporal lobe rather than prefrontal cortex.[36] However, variants capturing the set-encoding and response requirements of the SIRP are potentially feasible and valuable.

Measurement Properties. As described above, the response properties of the SIRP are well characterized on the basis of extensive study of healthy individuals.[12] The slope of RT as a function of memory load on the SIRP is relatively free from behavioral practice effects. Analysis of the data from 7 healthy subjects who performed approximately 1645 trials of a variable set version of the SIRP at 3 levels of WM load during 30 consecutive daily sessions indicated that although the intercepts decreased with practice, the slopes did not change.[37] A multisite reliability study of fMRI activation during the version of the SIRP proposed here found that both behavior and activation reliable across sites with different scanners and field strengths.[38] Ten healthy individuals traveled to 4 different sites and were scanned while performing the SIRP. The load dependence (ie, slope) and magnitude of activation in 18 anatomically and functionally defined regions of interest, which included the DLPFC, showed far greater between-subject variability than across-site variability. These findings suggest that the SIRP is readily adaptable to repeat and multisite studies of WM. Finally, a test-retest reliability study of the SIRP in controls and in patients with schizophrenia was also conducted.[39] RT was highly reliable in both groups and the difference in the mean RT across sessions was close to zero. Patients were reliable with regard to ER. Controls performed near ceiling levels during both sessions, and this restricted range of errors resulted in a low intraclass correlation. While the magnitude of activation in key regions of the WM network was highly reliable in controls, patients showed poor reliability. The unreliable brain activation within-subjects did not appear to reflect motion or other artifacts and occurred despite reliable task performance across sessions and stable clinical status suggesting that it may reflect real variability in regional brain recruitment over time. As is often the case, patients also showed a higher degree of within-subject variability in RT within each session.

Future Directions. There is strong evidence that the proposed adaptation of the SIRP elicits specific deficits in schizophrenia at the behavioral and neural levels. However, additional modifications are needed to specific assess interference control, as has been done in other variants of the SIRP in healthy adults.[21] It will be important to investigate how both behavior and patterns of brain activation on the SIRP vary in response to pharmacological and other types of intervention.

Capacity in WM

The construct of WM capacity was not selected for further examination at the initial CNTRICS meeting, which considered which constructs were ripe for translation and relevant to schizophrenia. The concept of WM capacity has received considerable attention in the cognitive science literature.[40] However, there was relatively little work on the "neurobiological" mechanisms constraining WM capacity at the time of the first meeting, and it felt premature to focus on capacity as a construct for the purposes of CNTRICS. It is very clear that the issue of capacity is highly relevant to understanding WM in schizophrenia because numerous studies have shown that individuals with schizophrenia show reduced WM capacity, eg.[41] At the final discussion period of the sixth CNTRICS meeting, the question of measuring capacity in schizophrenia was raised by a number of attendees. It was pointed out that a good deal of work on the neurobiology of WM capacity had been published since the first CNTRICS meeting and that this construct was now ripe for translation. Further, excellent behavioral and imaging biomarker measures of capacity exist. Thus, it was recommended that measures of WM capacity be pursued as imaging biomarkers in work on the etiology and treatment of schizophrenia, in addition to measures of goal maintenance and interference control. Here, we present a very brief overview of the work on the neural bases of WM capacity and describe one measure of WM capacity that has been used frequently in

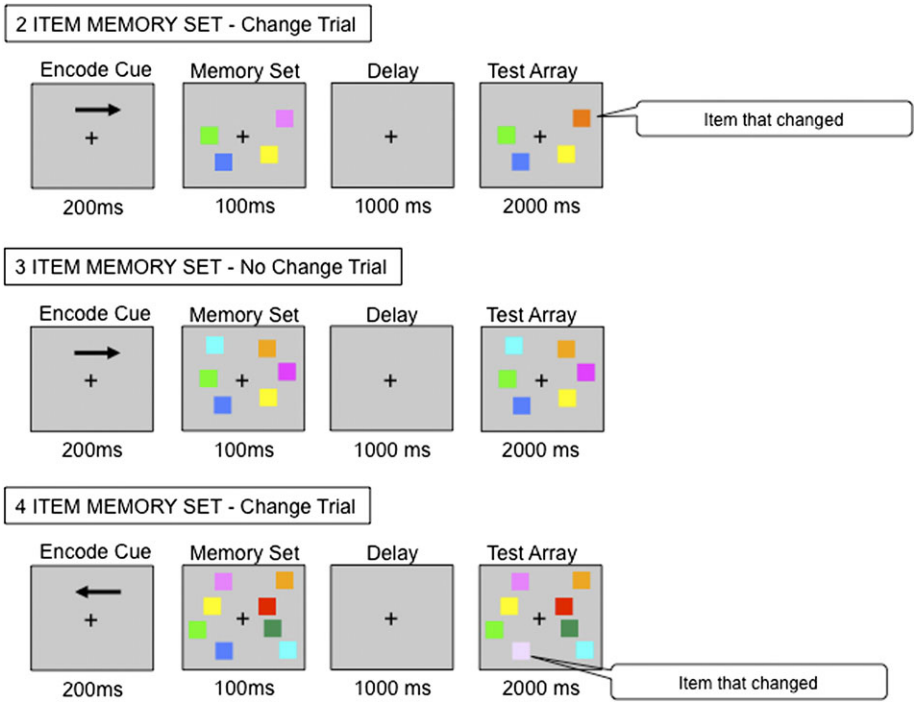

Fig. 3. Example schematic of one version of the Change Detection Task that can be used to measure contralateral delay-related activity. At the start of each trial, participants are presented with a cue indicating whether they should remember the items in the left or right visual hemifield. After a delay, they are presented with a test array and asked to indicate whether any of the items in the to be remembered hemifield changed in color. Half of the trials contain no changes (eg, middle panel) and half show changes, which occur only in the to be remembered field (eg, top panel). Capacity demands are varied by increasing the number of items in the encoding set.

both the basic cognitive neuroscience literature and which has been applied in schizophrenia.

Neural Systems of WM Capacity. Although for many years, it was thought that the capacity of WM was 7 plus or minus 2, more recent work has shown that when the contributions of rehearsal, grouping, and chunking are reduced, WM capacity is in the range of 3–5 items.[40] Several different lines of research point to the parietal cortex as a key node in the WM network that drives these capacity limitations. First, work in patients with lesions to posterior parietal cortex have shown that these patients show severe reductions in performance on spatial short-term memory or WM capacity tasks, eg,[42] though it is not clear whether this is also true for WM for other features, such as colors or shapes.[42] Second, work with ERP measures have shown sustained responses from posterior parietal cortex that track the number of items in visual WM and correlate strongly with individual differences in capacity (see below for additional details), eg.[43] Third, fMRI work has also shown that activity in bilateral intraparietal/intraoccipital sulci precisely tracks with visual WM load[44] and that individual differences in visual WM capacity are correlated with individual differences in parietal cortex activity.[45]

These findings regarding the role of parietal cortex in WM capacity raise the question of what coding or signal properties of the parietal cortex are responsible for this limitation. One proposal has been that lateral inhibition mechanisms involved in neuronal representation in parietal cortex limit the number of items that can be simultaneously maintained, with the added proposal that prefrontal mechanisms can help increase capacity by virtue of enhanced excitatory input that competes with lateral inhibition mechanisms.[46] Alternatively, it has also been proposed items are maintained in WM as unique patterns of coordinated firing across many neurons.[47] In such models, the number high-frequency oscillations (ie, gamma range) that can be embedded in a lower frequency oscillation (eg, theta) determines the number of distinct items that can be maintained memory.[47]

Measures of WM Capacity. Behaviorally, there are a number of different measures that have been used to assess capacity in WM, including verbal and nonverbal span tasks, Nback tasks, SIRP, and change detection tasks. One challenge with many of these tasks, such as digit span tasks or SIRP tasks with verbalizable materials, is that participants can use chunking or rehearsal mechanisms to modulate the number of items that can be maintained in WM. As noted above, Nback tasks tap many different aspects of WM (including temporal ordering) and do not isolate capacity per se. Spatial span tasks, while reducing the contribution of rehearsal or chunking, are not particularly amenable to an imaging biomarker use. Change detection tasks are a class of

capacity measures that reduce the contribution of chunking and rehearsal. In these tasks, participants are presented with an array of objects and then asked to detect a change in one or more features of the object after a short delay. The features could be color, shape, orientation, etc., and the number of objects can be varied across trials. These types of tasks have been used extensively in behavioral studies to characterize normative limits on WM capacity, eg,[48,49] and have been used to identify capacity reductions in schizophrenia, eg.[41] Furthermore, a variant of the paradigm has been developed as an imaging biomarker (see figure 3 for illustration). Participants are presented with a bilaterally symmetrical display of objects but cued to remember the items in either the left or right visual hemifield. During the delay period between the presentation of the memory set and the test array, a sustained negative-going voltage can be measured over the hemisphere contralateral to the visual field containing the to be remembered items (typically assessed as the difference in amplitude between the ipsilateral and contralateral hemispheres). The magnitude of the contralateral delay-related activity varies with the number of items being held in WM, eg.[43] The same basic paradigm, but without cuing of a single hemifield, leads to analogous results in fMRI experiments.[47]

Future Directions. Both the behavioral and imaging biomarker versions of the change detection task are excellent measures of WM capacity and functional brain activity associated with capacity limits. This task has already shown sensitivity to deficits in WM capacity in schizophrenia. However, little is known about the psychometric properties of either the behavioral or imaging biomarker version, and more work is needed to determine whether it is sensitive to psychological or pharmacological manipulation. An animal version of the task has been used in pigeons,[50] but additional work is needed to demonstrate that it can also be used in rodents and/or primates.

General Conclusion. This article was designed to provide the reader with a brief overview of the data used to select among the different tasks nominated as imaging biomarker measures of the constructs of goal maintenance and interference control in WM. In addition, it provided a brief overview of the reevaluation of the construct of capacity in WM, and initial suggestions for a promising measure that could be used both behaviorally and as an imaging biomarker. One of the clear next steps in work in developing these imaging biomarkers for use in clinical trials in schizophrenia is work examining and enhancing the psychometric properties of these tasks, as few imaging biomarkers have been systematically studied for characteristics such as test-retest reliability, length, sensitivity, etc. In addition, more work is needed to determine whether these biomarkers are sensitive to pharmacological or psychological manipulations, as will be necessary if they are to be useful in a clinical trials context. The potentially utility of these measures in helping to develop effective treatments for cognitive impairment in schizophrenia make such efforts highly important in order to move the field forward. These measures may also be very helpful in elucidating the neural mechanisms that contribute to schizophrenia. As has been discussed by many researchers and theorists, WM deficits may be a core aspect of cognitive impairment in schizophrenia, and thus further examination of their psychological and neural bases may provide rich clues as to the pathophysiology of the illness that could be translatable into more effective prevention or intervention approaches.

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