Cognitive [Computational] Neuroscience Test Reliability and Clinical Applications for Serious Mental Illness (CNTRaCS) Consortium: Progress and Future Directions

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Abstract The development of treatments for impaired cognition in schizophrenia has been characterized as the most important challenge facing psychiatry at the beginning of the twenty-first century. The Cognitive Neuroscience Treatment Research to Improve Cognition in Schizophrenia (CNTRICS) project was designed to build on the potential benefits of using tasks and tools from cognitive neuroscience to better understanding and treat cognitive impairments in psychosis. These benefits include: (1) the use of fine-grained tasks that measure discrete cognitive processes; (2) the ability to design tasks that distinguish between specific cognitive domain deficits and poor performance due to generalized deficits resulting from sedation, low motivation, poor test taking skills, etc.; and (3) the ability to link cognitive deficits to specific neural systems, using animal models, neuropsychology, and functional imaging. CNTRICS convened a series of meetings to identify paradigms from cognitive neuroscience that maximize these benefits and identified the steps need for translation into use in clinical populations. The *Cognitive Neuroscience Test Reliability and Clinical Applications for Schizophrenia (CNTRaCS) Consortium* was developed to help carry out these steps. CNTRaCS consists of investigators at five different sites across the country with diverse expertise relevant to a wide range of the cognitive systems identified as critical as part of CNTRICs. This work reports on the progress and current directions in the evaluation and optimization carried out by CNTRaCS of the tasks identified as part of the original CNTRICs process, as well as subsequent extensions into the Positive Valence systems domain of Research Domain Criteria (RDoC). We also describe the current focus of CNTRaCS, which involves taking a computational psychiatry approach to measuring cognitive and motivational function across the spectrum of psychosis. Specifically, the current iteration of CNTRaCS is using computational modeling to isolate parameters reflecting potentially more specific cognitive and visual processes that may provide greater interpretability in understanding shared and distinct impairments across psychiatric disorders.

Keywords CNTRaCS · CNTRICS · Cognitive neuroscience · Positive valence systems · Schizophrenia

Cognitive impairments in schizophrenia are present prior to illness onset (see Karcher et al.'s chapter in this volume), persist throughout the lifespan, are associated with poor outcome and functional disability, and are largely treatment refractory. Hence, development of treatments for impaired cognition in schizophrenia has been characterized as the most important challenge facing psychiatry at the beginning of the twenty-first century (Carter and Barch 2007). The past several decades have seen a rapidly growing understanding of the neurobiology and neuropharmacology of cognition, and research has identified many molecular targets for enhancing cognitive processing in schizophrenia and other psychiatric disorders (Arnsten 2004; Friedman 2004; Lewis et al. 2004; Martin et al. 2004; Moghaddam 2004; Roth et al. 2004; Tamminga 2006). However, despite this growing knowledge, there was no established mechanism for developing cognitive enhancing drugs for

schizophrenia until the National Institute of Mental Health (NIMH)-funded Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS, see Nuechterlein et al.'s chapter in this volume) initiative was created. The MATRICS (Green et al. 2004; Marder and Fenton 2004) process brought together academia, the pharmaceutical industry, and the Food and Drug Administration to: (1) identify cognitive domain targets in schizophrenia; (2) identify promising molecular targets to enhance those cognitive domains; and (3) develop a process by which new therapeutic agents could be approved for the treatment of cognition in schizophrenia.

One of the challenges MATRICS faced was the need to produce a consensus based set of cognitive measures quickly. Thus, MATRICS selected standardized tests with well-known and strong measurement properties (test-retest reliability, low practice effects, etc.). As such, the measurement approach in the MATRICS battery primarily reflects the experience of the field with clinical neuropsychological tests used in the clinical trials of atypical antipsychotics during the 1980s and 1990s. Measures derived from cognitive neuroscience were considered, but were not included primarily because they did not have already established measurement properties. The Cognitive Neuroscience Treatment Research to Improve Cognition in Schizophrenia (CNTRICS) project grew out of the final MATRICS meeting, where the potential benefits of using tasks and tools from cognitive neuroscience were broadly acknowledged. These benefits include: (1) the use of fine-grained tasks that measure discrete cognitive processes; (2) the ability to design tasks that distinguish between specific cognitive domain deficits and poor performance due to generalized deficits resulting from sedation, low motivation, poor test taking skills, etc.; and (3) the ability to link cognitive deficits to specific neural systems, using animal models, neuropsychology, and functional imaging. Measuring the function of specific cognitive systems 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 specific cognitive systems. Many such targetable systems, such as working memory and episodic memory (WM and EM, respectively), attention, perceptual processing, and cognitive control are conserved across many mammalian species and measurable using parallel versions of experimental cognitive tasks. CNTRICS was developed collaboratively with the leadership of the NIMH including Drs. Robert Heinssen, Director Tom Insel, and the late Wayne Fenton and supported by two R13 conference grants.

At the first meeting, CNTRICS identified a set of constructs across six cognitive systems to be targeted (Carter and Barch 2007; Carter et al. 2008), including executive control, WM, EM, attention, and perception. At the second meeting measurement issues were laid out together with strategies for addressing them in future research (Barch and Carter 2008). At the third meeting tasks were identified that were promising measures of these cognitive systems (Barch et al. 2009a, b). Task selection was guided by the following principles: (1) tasks have strong construct validity from cognitive neuroscience as measures of the cognitive processes to be targeted; (2) there are strong data from cognitive neuroscience linking the

processes engaged by the task to specific neural systems; (3) the tasks have designs that will allow us to distinguish between a specific cognitive deficit and a generalized deficit; (4) tasks are readily incorporated into functional imaging (EEG and fMRI) studies that can measure medication effects on cognition related brain activity; (5) tasks assay distinct neural systems, and provide coverage of deficits in both early "bottom-up" and later "top-down" processes in order to enhance the utility of these tools for different pharmacological agents; and (6) where possible tasks have the possibility for use across-species. These tasks are known to be sensitive to deficits in schizophrenia, though in some cases the tasks needed to be studied using new parameters designed to meet the six properties outlined above.

After initial CNTRICS meetings, the NIMH issued a Request for Proposals to fund research that would optimize and psychometrically evaluate these tasks identified through the CNTRICs process. In response to this call, the *Cognitive Neuroscience Test Reliability and Clinical Applications for Schizophrenia (CNTRaCS) Consortium* was developed consisting of investigators at five different sites across the country with diverse expertise relevant to a wide range of the cognitive systems identified as critical as part of CNTRICs. These five sites were Washington University in St. Louis (led by Deanna Barch), Maryland Psychiatric Research Center (led by Jim Gold), Rutgers University (led by Steve Silverstein), the University of California at Davis (led by Cameron Carter and Daniel Ragland), and the University of Minnesota (led by Angus MacDonald). Here, we report on the progress and current directions in the evaluation and optimization carried out by CNTRaCS of the tasks identified as part of the original CNTRICs process, as well as subsequent extensions into the Positive Valence systems domain of Research Domain Criteria (RDoC). All tasks and a description of the validation process are available for download at https://cntracs.ucdavis.edu/. We end by discussing the current focus of CNTRaCS, which involves taking a computational psychiatry approach to measuring cognitive and motivational function across the spectrum of psychosis. Specifically, the current iteration of CNTRaCS is using computational modeling to isolate parameters reflecting potentially more specific cognitive and visual processes that may provide greater interpretability in understanding shared and distinct impairments across psychiatric disorders.

1 Goal Maintenance

We define goal maintenance as 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 (Cohen and Servan-Schreiber 1992; Kane and Engle 2000, 2002, 2003; Kane et al. 2001a, b; Miller and Cohen 2001; Engle and Kane 2004; Barch et al. 2009a, b). Goals also include task set representations that help determine what information is relevant for the current contents of WM, also referred to as "context" information (Cohen and

Servan-Schreiber 1992). Active goal maintenance has been linked to the function of dorsolateral prefrontal cortex (DLPFC), with additional work implicating dopaminergic inputs to DLPFC are critical as well (though recent work has also specified an important role for both glutamate (Durstewitz and Gabriel 2007) and norepinephrine (Arnsten 2004)). Such mechanisms by which goals could be actively maintained and bias ongoing information processing have been explicitly implemented in biologically plausible computational models designed to formalize the interactions between prefrontal and basal ganglia systems in goal maintenance (Braver et al. 1995; Anderson et al. 1996; Just et al. 1996; Braver and Cohen 2000; Miller and Cohen 2001; Hazy et al. 2007; Collins and Frank 2013). Further, a number of functional imaging studies revealed activation of DLPFC when individuals are required to maintain goals in WM (Barch et al. 1997; MacDonald et al. 2000; Passingham and Sakai 2004; Fassbender et al. 2006). Thus, this construct has confirmed validity at both the psychological and neural levels of analysis.

As previously reviewed (Barch et al. 2009a, b), numerous studies provide evidence that both medicated and unmedicated individuals with schizophrenia have difficulties with goal maintenance, at both acute and chronic stages of the illness (Servan-Schreiber et al. 1996a, b; Schooler et al. 1997; Stratta et al. 1998; Cohen et al. 1999; Javitt et al. 2000; Stratta et al. 2000; Barch et al. 2001; Chen et al. 2001; Henik et al. 2002; Bagner et al. 2003; MacDonald and Carter 2003; Barch et al. 2004a, b; Henik and Salo 2004; Holmes et al. 2005; Ettinger et al. 2006; Lee and Park 2006; Radant et al. 2007; Wilde et al. 2007). In addition, goal maintenance deficits are found in first-degree relatives of individuals with schizophrenia (MacDonald et al. 2003; Calkins et al. 2004; Delawalla et al. 2007), and in individuals with schizotypal personality disorder (Barch et al. 2004a, b; Calkins et al. 2004), indicative of a potential genetic and broad-based underlying mechanisms. This construct was identified for measurement development for three of the six domains addressed by CNTRICS ((attention, WM, and executive functions (Carter et al. 2008)). That is, deficits in goal maintenance were thought to be responsible for many of the impairments observed across attention, WM, and executive control in schizophrenia, suggesting that this may be a critical core deficit in the illness (Carter et al. 2008).

One task used to understand the psychological and neural mechanisms underlying goal maintenance is the expectancy manipulation of the traditional AX-CPT (Servan-Schreiber et al. 1996a, b), which has been used in both its original form (AX-CPT) and in a form (called the dot pattern expectancy task, or DPX, see below) that uses non-verbal stimuli (reducing confounds associated with native language and literacy, and decrease administration time (MacDonald et al. 2005a, b)). In the expectancy AX-CPT, participants view a series of letters one at a time. They respond with the non-target button to every letter except X when it follows an A, which requires a target response. The vast majority of trials are A-then-X trials, creating a prepotent pattern of responding. Whether the cue was an A or any other letter (hereafter called B) provided the context for preparing a response. In BX trials, which occurred ~10% of the time, the B provided the context that the subsequent X was not a target, although generally X's are valid targets. Individuals with

schizophrenia had difficulty representing and maintaining this context and were more likely to be lured into mistaking this invalid X for a target (BX maintenance error). Thus, this condition tested the ability to maintain crucial goal information. In AY trials, which also occurred ~10% of the time, the A provided the context that the subsequent stimulus was likely to be a valid target. When any invalid probe occurred (hereafter Y), individuals who have prepared for a target response have to overcome that prepared response. Thus, the expectancy AX task can produce a double-dissociation in performance whereby individuals with a goal maintenance deficit show impaired performance on BX trials, whereas those with intact goal maintenance but poor cognitive control perform poorly on AY trials.

CPT paradigms are domain general, and any number of stimuli can be defined as valid cues or probes. A limitation of using letter stimuli is that a very strong prepotency, many trials, and a longer cue-probe delay are required to identify a specific deficit associated with schizophrenia. Such tasks can take up to 45 min (Cohen et al. 1999; MacDonald et al. 2003). This limitation may be related to the ease with which over-learned letter stimuli are stored. Thus, we developed the DPX, which uses under-learned dot pattern stimuli (originally based on Braille letter patterns). The DPX had the added advantage of making AY trials harder for controls, thereby increasing the likelihood that differences the BX condition would be interpretable as a specific deficit in goal maintenance (MacDonald et al. 2005a, b). Confirmatory factor analysis supported the convergent validity of the letter version of the expectancy AX and the formally equivalent DPX (MacDonald et al. 2005a, b).

CNTRaCS chose this DPX paradigm because it fulfills the criteria the field (in CNTRICS Meeting two), identified as important for task selection (Barch et al. 2009a, b). The AX-CPT was discussed during MATRICS as a candidate task but due to its long duration of administration and unknown psychometric properties further consideration was deferred. CNTRaCS compared five DPX versions that manipulated the strength of prepotency and the length of the interstimulus interval (ISI) between cues and probes. As shown in Fig. 1, results indicated that the best compromise between task duration and interpretability occurred on a version with a short ISI (2,000 ms vs. 4,000 ms) and a strong prepotency (69% "AX" trials, which elicited clear deficits in both schizophrenia and schizoaffective disorder (Henderson et al. 2012). This version of the task correlated with negative symptoms, daily living skills, and functional status (Gold et al. 2012a, b). In addition, a subsequent CNTRaCS test-retest study indicated that the optimized DPX shows acceptable internal consistency (Henderson et al. 2012) and good to excellent test-retest reliability (Strauss et al. 2014), as well as modest practice effects. In addition, there is a version of the DPX for use in primates (Blackman et al. 2016).

In subsequent work, CNTRaCS was funded to develop the DPX (and AX-CPT) into imaging biomarkers that could be used to assess the neural systems supporting goal maintenance and identify the neural correlations of impairments in goal maintenance. The signature of goal maintenance is activation of DLPFC (BA 9/46) in conditions where active representation is necessary for task appropriate behavior, as seen in numerous AC-CPT studies (Barch et al. 1997; Braver and Bongiolatti 2002). Individuals with schizophrenia also show consistent evidence of impaired prefrontal

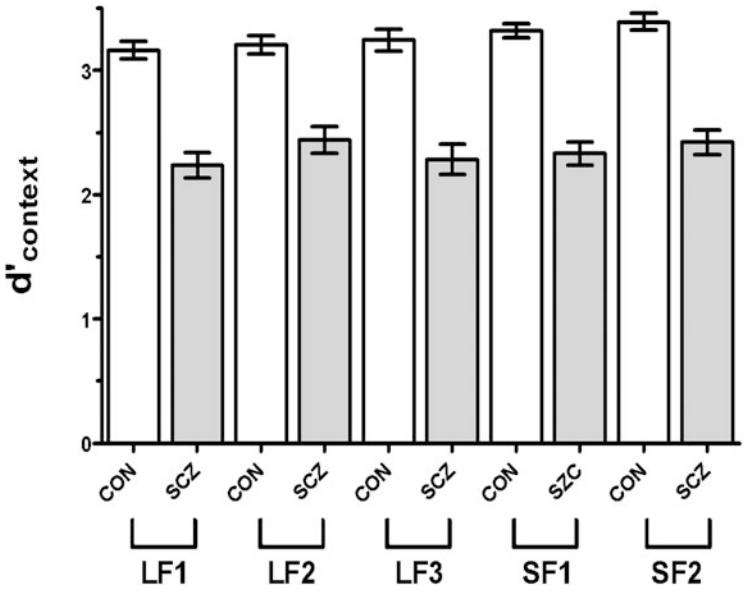

Fig. 1 Mean and standard error of $d'_{context}$ for patient and control groups for each of five DPX tasks. LF1 (long form 1) and SF1 (short form 1) had 69%, LF2 and SF2 62%, and LF3 58% AX trials. Reprinted with permission from Henderson et al. (2012)

activity, particularly in DLFPC regions, during tasks requiring goal maintenance (Barch et al. 2001; Holmes et al. 2005; MacDonald et al. 2005a, b; Harrison et al. 2006; Tu et al. 2006; Van Snellenberg et al. 2006). Again, first-degree relatives of individuals with schizophrenia also showed impaired DLPFC activation during goal maintenance (MacDonald et al. 2006; Delawalla et al. 2007). Evidence from the CNTRaCS Imaging Biomarker study indicated that both of the CNTRaCS AX-CPT and DPX tasks robustly engage the frontal-parietal network in conditions that require the use of goal information to guide behavior (Lopez-Garcia et al. 2016). Consistent with early work using the AX-CPT (Barch et al. 1999, 2001; Holmes et al. 2005; MacDonald et al. 2005a, b), as shown in Fig. 2, the CNTRaCS imaging DPX robustly identified reduced activation in dorsal frontal and parietal regions among individuals with schizophrenia (Poppe et al. 2016). Thus, the DPX provides a novel symbol-agnostic method to measure DLPFC activity during goal maintenance in individuals and is sensitive to deficits in individuals with schizophrenia.

2 Relational Encoding and Retrieval in Episodic Memory

Another cognitive domain identified by CNTRICS is that of EM, specifically relational encoding and retrieval. EM depends on representations that link together information about items and the context that they were encountered in, as well as

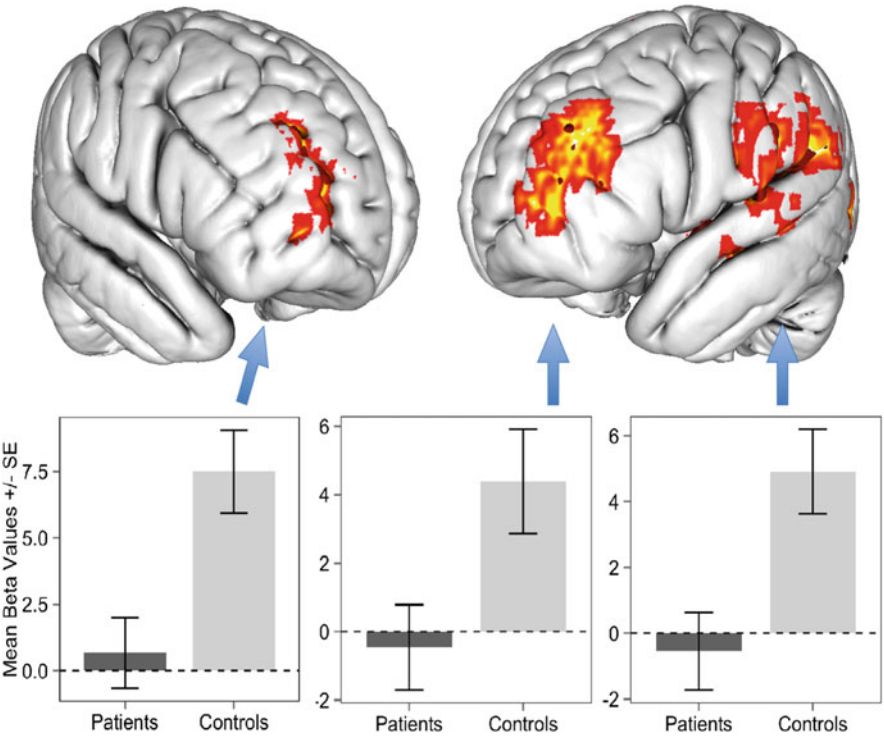

Fig. 2 Whole brain functional magnetic resonance imaging (fMRI) GLM results. Beta values represent B Cues – A Cues contrast. Regions with greater activation in healthy controls (HC) than schizophrenia (SCHIZOPHRENIA; 3 clusters). Reprinted with permission Poppe et al. (2016)

strategies that help us form these representations. For instance, one can use "item-specific" encoding strategies that focus attention on distinctive aspects of particular items (e.g., pleasantness or animacy judgments), or "relational" encoding strategies that focus attention on relationships between items encountered at a particular moment (e.g., imagine two items interacting, or link two or more words in the context of a sentence or story (Bower 1970a, b; Hunt and Einsten 1981; Hunt and McDaniel 1993)). Relative to item-specific processing, relational processing disproportionately depends on DLPFC (Postle et al. 1999), and engagement of the DLPFC during relational WM processing predicts successful EM for inter-item associations (Blumenfeld and Ranganath 2006, 2007; Murray and Ranganath 2007). There is near consensus that the hippocampus is essential for EM, supporting recollection of contextual information associated with specific items, particularly relationships between items (Ranganath 2010). Available evidence, therefore, indicates that the construct of relational encoding and retrieval has validity at both cognitive and neural levels of analysis and is supported by both hippocampal- and DLPFC mediated mechanisms.

Individuals with schizophrenia have pronounced EM impairment (Heinrichs and Zakzanis 1998; Aleman et al. 1999; Ranganath 2010), with evidence of hippocampal abnormalities (Heckers and Konradi 2010; Benes 2015; Roeske et al. 2021), but the pattern is task-dependent (Pelletier et al. 2005). Like frontal lobe lesion individual, individuals with schizophrenia become more impaired as retrieval tasks become less structured. Meta-analytic reviews demonstrate moderate-to-large effect sizes of schizophrenia on free recall tasks, medium effects on cued recall tasks, and lesser impairments during recognition testing (Paulsen et al. 1995; Aleman et al. 1999). Individuals with schizophrenia also fail to spontaneously use item-specific semantic information to categorize related word lists during initial encoding (Gold et al. 1992; Paulsen et al. 1995; Iddon et al. 1998). This failure appears due to difficulty self-generating item-specific organizational strategies rather than lack of semantic knowledge (Brebion et al. 1997; Iddon et al. 1998; Stone et al. 1998), since recognition can be remediated by instructing individuals to make semantic decisions about individual words on a learning list (McClain 1983; Brebion et al. 1997; Stone et al. 1998; Ragland et al. 2003; Bonner-Jackson et al. 2005). However, individuals with schizophrenia continue to show impairment on tasks that require relational encoding (Titone et al. 2004; Ongur et al. 2006) and may not benefit from being provided with a relational encoding strategy, either because of specific difficulties implementing DLPFC relational control functions (Ragland et al. 2007) or because of impaired hippocampally-mediated binding functions (Heckers et al. 1998; Weiss et al. 2003; Heckers 2004; Weiss et al. 2004).

Many cognitive neuroscience paradigms designed to assess relational encoding and retrieval suffer from a problem that limits their application to clinical populations – they leave the nature of the encoding strategy up to the individual, opening the possibility that poor task performance simply reflects a failure to apply relational processing, rather than a fundamental deficit in the ability to engage in such processing. Ranganath and colleagues developed a task to investigate cognitive and neural mechanisms underlying relational encoding and retrieval (Blumenfeld and Ranganath 2006) that explicitly controls the type of relational processing in which participants engage. This paradigm did a good job meeting the CNTRICS selection criteria of strong construct validity, a specific neural mechanism, and appropriateness for functional imaging.

As shown in Fig. 3, CNTRaCS created a variation of the Ranganath paradigm named the relational and item-specific encoding and retrieval task (RiSE). This task manipulated encoding by requiring participants to decide whether stimuli are "living/nonliving" (item-specific) or whether one stimulus fits inside the other (relational). This task also allows one to estimate familiarity (F) and recollection (R) by examining receiver operator characteristics (ROC) and assessing item (old or new judgment) and associative (were these items presented together or not) recognition. CNTRaCS compared word and object versions of the RiSE, with objects more effective in identifying impairments in relational encoding and retrieval in schizophrenia. Specifically, CNTRACS studies (Ragland et al. 2012) confirmed that individuals with schizophrenia had a disproportionate recognition deficit following relational-versus item-specific encoding, most striking for familiarity-based

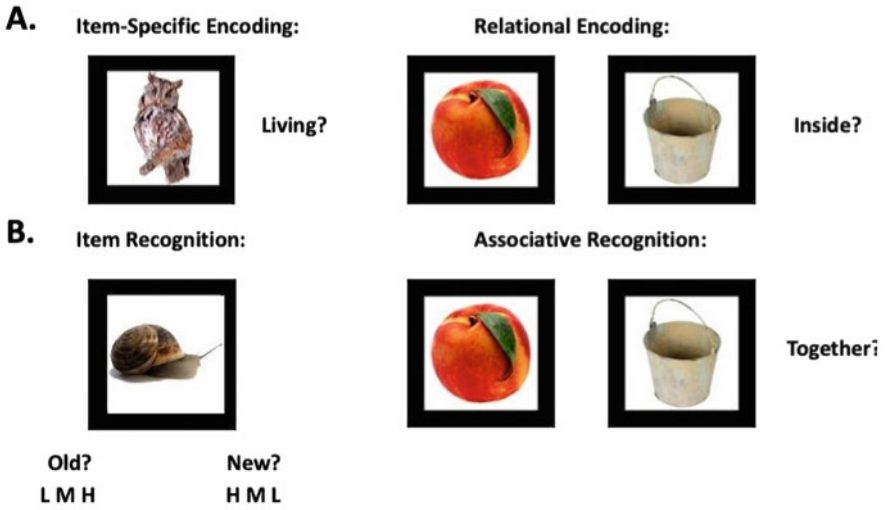

Fig. 3 Illustration of item-specific and relational test procedures and task stimuli. (**a**) Memory encoding, (**b**) Memory retrieval. Reprinted with permission from Ragland et al. (2012)

retrieval. Moreover, RiSE performance was positively correlated with functional abilities and had good internal consistency, retest reliability (more so for item than associative recognition), and good alternate-form reliability (Ragland et al. 2012). Further, CNTRaCS created three parallel versions of the RiSE with good psychometric properties to enable repeated testing. Thus, this task is useful for both group studies, individual differences, and treatment studies.

Like goal maintenance, CNTRaCS was supported to create a version of the RiSE task for use as an imaging biomarker measure. Murray and Ranganath (Murray and Ranganath 2007) found that activity in the DLPFC was higher during relational than item-specific encoding and specifically predicted successful memory for associations amongst items. Activity in the VLPFC also increased for relational encoding, but was nonspecific and predicted success in item-specific and associative recognition conditions. This work suggests that DLPFC may contribute to EM through its role in active processing of relationships during encoding and that DLPFC will show greater activation in relational than item encoding. In contrast, the VLPFC may have a more general role in encoding processes for both relational and item encoding (Blumenfeld and Ranganath 2007). The RiSE was also designed to reveal anatomical dissociations within the medial temporal lobe by examining separate components of episodic retrieval. The hippocampus and parahippocampal cortex (PHC) play central roles in creating memories of the relationships between specific items and the context in which they were encountered (Eichenbaum et al. 2007; Ranganath 2010) and then retrieving these contextual details to support associative recognition or recollection of the event (Davachi 2006). As shown in Fig. 4 and described above, consistent with these hypotheses, we found that relational versus item-specific encoding activated both DLPFC and VLPFC prefrontal cortex, but activity was

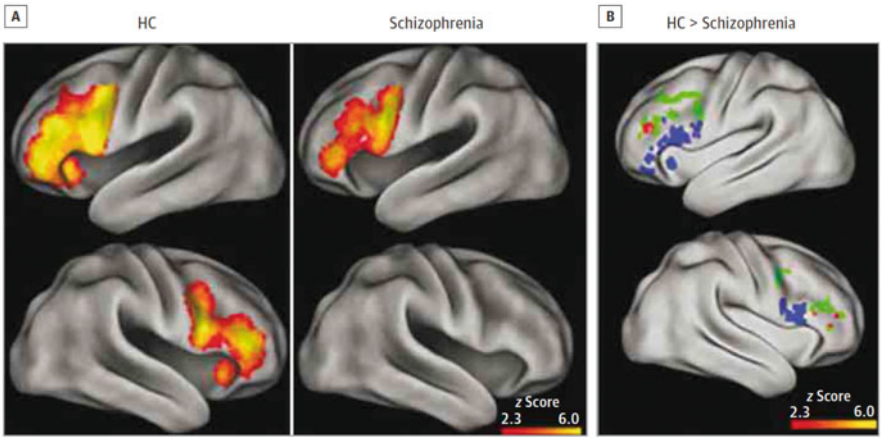

Fig. 4 Brain activation in RiSE task in schizophrenia. (**a**) Surface rendering of left (top) and right (bottom) hemisphere PFC activation shown separately for healthy controls (HC) and individuals with schizophrenia. Hotter colors reflect greater activation (range, $z = 2.3$-6.0). (**b**) Significant group differences (HC-schizophrenia) in dorsolateral PFC activation during relational versus item-specific encoding in left (top) and right (bottom) hemispheres. Group differences are indicated in red, with hotter colors reflecting greater activation (range, z 2.3-6.0) and are overlaid on dorsolateral PFC (green) and ventrolateral PFC (blue) regions of interest to illustrate the regional specificity of prefrontal dysfunction in schizophrenia. Reprinted with permission from Ragland et al. (2012)

reduced in schizophrenia relative to healthy controls only in the DLPFC (Ragland et al. 2015). Retrieval success (hits > misses) was associated with activation of the hippocampus in controls during associative recognition and item recognition following relational encoding and was reduced in individuals with schizophrenia for item recognition following relational encoding. Thus, these data support the construct validity of the RiSE in revealing expected DLPFC and medial temporal lobe memory effects during specific encoding and retrieval conditions. Group differences support the presence of a disproportionate memory deficit in schizophrenia for relational versus item-specific information, accompanied by regionally and functionally specific deficits in DLPFC and hippocampus activation.

3 Gain Control

A critical component of perception highlighted at the first CNTRICS meeting was gain control, which refers to processes that amplify or attenuate overall levels of neural activity to optimize operation of systems with limited, dynamic signaling range. Sensory gain control operates via intracellular mechanisms, direct excitatory and inhibitory connections between neurons, and feedback. Gain control mechanisms have been demonstrated using various behavioral tasks, including those involving pop-out phenomena (where neurons coding similar features inhibit each

other, leading to increased salience of a single different element) (Derrington 1996), effects of surrounding contrast on contrast thresholds (Chubb et al. 1989), texture segregation (where texture elements near texture borders are increased in salience) (Nothdurft et al. 2000), and figure-ground segregation (Lamme 1995). Moreover, there is convergence between theoretical work (e.g., Heeger 1992), psychophysical studies (e.g., Foley 1994), electrophysiology (Bonds 1989, 1991), and functional MRI (Zenger-Landolt and Heeger 2003), in supporting the existence of gain control mechanisms and their effects on neurons in the visual cortex.

Gain control impairments in individuals with schizophrenia are found for both vision (e.g., Yeap et al. 2006) and audition (e.g., Javitt et al. 1997). For example, individuals demonstrate less visual suppression (as assessed by contrast sensitivity functions) due to the effects of surrounding contrast (Dakin et al. 2005; Linares et al. 2020). In addition, individuals with schizophrenia show clear, magnocellular (M)-pathway dysfunction, typically as assessed by either contrast sensitivity or backward masking functions (Cadenhead et al. 1998; Slaghuis and Thompson 2003; Keri et al. 2004; Butler et al. 2005, 2007; Kim et al. 2005, 2006a, b). The M-pathway has several properties (speed of processing, low spatial resolution) that suggest it is a physiological substrate for gain control (Lennie 1980) so that deficits in M-processing may be the physiological basis for gain control abnormalities in schizophrenia. Mechanisms of gain control dysfunction also include NMDA and GABA-ergic dysfunction. Indeed, NMDA dysfunction appears to be linked to gain control in the M-pathway, and it is linked to schizophrenia (Javitt and Zukin 1991). There is also evidence that gain control deficits are important in outcome. For instance, impaired contrast detection in steady-state and transient visual evoked potential studies is related to poorer functional outcome in schizophrenia as assessed with the Problem Solving Factor of the Independent Living Scales (ILS) (Schechter et al. 2005). Finally, abnormal contrast sensitivity and backward masking functions are linked to negative symptoms and poor treatment outcome in individuals with schizophrenia (Slaghuis 1998). Thus, aspects of gain control may be an important target for overall treatment in individuals with schizophrenia.

There are a number of different approaches to measuring gain control. One such approach – referred to as the Contrast-Contrast Effect task is to study the perception of contrast utilizing an illusion in which the contrast of the elements in a small target circle appears reduced when presented within a high contrast surround compared to when the same target is presented in isolation (Chubb et al. 1989). When asked to match a variable contrast patch to the central patch, controls indicated that the central patch had a substantially lower contrast than it actually did, reflecting affected gain control. Individuals with schizophrenia were less susceptible to the illusion and in fact 12 of 15 individuals were more accurate than the most-accurate control (Dakin et al. 2005). These results are consistent with decreased center-surround antagonism and hence decreased gain control in schizophrenia individuals.

Given that this approach affords the ability to rule out a generalized deficit interpretation, CNTRaCS used the Contrast-Contrast Effect task (Saccuzzo and Schubert 1981; Green and Walker 1984) in the first set of studies. More specifically, we compared versions of the Contrast-Contrast Effect task that manipulated duration

and included catch trials to measure off-task performance (attention lapsing) (Barch et al. 2012). In the first CNTRaCS study using this task, we were able to replicate previous findings of reduced surround effects in schizophrenia (a putative indication of reduced gain control), but found that such effects were almost entirely accounted for by off-task performance as measured by lapses on easy catch trials. In a subsequent test-retest reliability study, the gain control task once again failed to provide evidence of impairments in schizophrenia that were independent of attention lapsing. Thus, the CNTRaCS consortium ultimately did not recommend the version of this task to assess impaired gain control in schizophrenia.

4 Visual Integration

Visual integration includes processes beyond the registration of color, orientation, motion, and depth cues that can bind these features to create higher-level, emergent, holistic, representations (i.e., shapes, and eventually objects) that are suitable to guide behavior. Integration occurs both via long-range lateral connections between feature detectors within early visual cortex areas and via recurrent innervation of visual cortex by temporal visual regions involved in object recognition, and frontal and parietal regions supporting visual attention. Integration is relevant to phenomena such as gestalt perception, object recognition, and coherent motion perception. The existence of integrative mechanisms in vision is supported by data from a variety of sources. First, animal studies (e.g., cats) using microelectrode recording demonstrate effects of information from outside of classical receptive fields on target processing (e.g., Kapadia et al. 1995). Second, psychophysical studies of perceptual organization in healthy humans (e.g., Pomerantz and Pristach 1989; Kovacs 1996) demonstrate integrative processing. Third, electrophysiological recording of healthy humans during visual integration tasks (e.g., Han et al. 2001, 2002) and fMRI studies of integration in healthy human subjects and in monkeys (e.g., Altmann et al. 2003; Kourtzi et al. 2003) all provide evidence of integrative mechanisms. Converging data from these lines of research indicate that, along the ventral visual stream from V1 to inferior and lateral temporal areas, receptive fields of cells become increasingly larger, more responsive to global stimulus features, and invariant with respect to retinotopic position of the stimulus. Data also indicate that the firing rates of these cells are increasingly more dependent on the extent to which sets of individual features possess statistical regularities indicative of a contour or shape (e.g., correlations between element orientations) (Kanwisher 2004).

Numerous studies demonstrate a reduction in visual feature integration abilities in individuals with schizophrenia (Silverstein et al. 2015a, b, 2020; Keane et al. 2016). Moreover, in several of these studies, the reduced ability to integrate information resulted in superior overall performance of the task compared to controls, in making decisions about individual features (see gain control section above). This superiority includes a reduced susceptibility to visual illusions in which the grouping of information interferes with accurate perception (Uhlhaas et al. 2006). Therefore,

evidence for impairments in visual integration is convincingly demonstrated independent of a generalized deficit (Knight and Silverstein 2001). Integration impairments in individuals with schizophrenia are demonstrated with both static (Silverstein et al. 2000) and moving cues (Chen et al. 2005). Furthermore, integration impairments in schizophrenia are disease-specific/medication independent as deficits are seen in unmedicated individuals (Uhlhaas et al. 2005; Uhlhaas and Silverstein 2005), with performance not correlated with medication dose in medicated individuals (Spencer et al. 2003, 2004).

Researchers typically measure visual integration by manipulating a single stimulus parameter and determine the effect of this manipulation on the ability to perceive stimulus configurations. The most common manipulations include those of contour element orientation and contour element spacing. CNTRaCS examined a version of the task that manipulated the orientation of the elements. Specifically, participants are asked to determine which direction an egg-shaped contour, made up of Gabor elements, is pointing. Gabor elements are Gaussian-modulated sinusoidal luminance distributions that closely model the known spatial frequency processing properties of cells in area V1. Therefore, use of Gabor elements provides superior measurement of orientation sensitivity, and grouping of orientation cues, compared to stimuli with unknown effects on V1 neurons (e.g., arbitrarily constructed lines and dots). The embedded contours in stimuli utilizing Gabor elements cannot be detected by purely local filters or by known types of orientation tuned neurons with large receptive fields (e.g., Dakin and Hess 1998). The long-range orientation correlations along the path of the contour can only be found by integration of local orientation measurements into an emergent shape representation. Numerous studies using such tasks have explored the conditions under which human observers perceive or do not perceive contours. CNTRaCS refers to this task as the Jittered Orientation Visual Integration (JOVI) task. Participants press one of two keys to indicate whether the shape was leftward or rightward pointing. Trials are blocked according to the amount of orientational jitter that was added to the contour elements: ±0°, 7–8°, 11–12°, 15–16°, 19–20°, or 23–24° (see Fig. 5). An advantage of having a broad range of jitter values is that one can plot each subject's complete psychometric function – from floor to ceiling. In the first CNTRaCS study with this task, we found prominent ceiling and floor effects and there were no between-group differences in threshold or slope (Silverstein et al. 2012). In a follow-up study, we utilized a narrower range of difficulty levels (eliminating 19–20°, or 23–24°) and found that patient thresholds were worse than those of controls (Silverstein et al. 2012). This difference in performance remained even when only the first half of the trials were analyzed and when we controlled for catch trials (Silverstein et al. 2012; Strauss et al. 2013). Thus, the JOVI provides a brief (six-minute), sensitive measure of visual integration deficits in individuals with schizophrenia. Accuracy on this task shows good test-retest reliability, though threshold estimates are less optimal in terms of test-retest reliability (Strauss et al. 2013).

CNTRaCS also aided in the creation of an imaging biomarker version of the JOVI. The contour integration task has demonstrated sensitivity to visual integration deficits in both anisometropic and strabismic amblyopia, disorders where integration

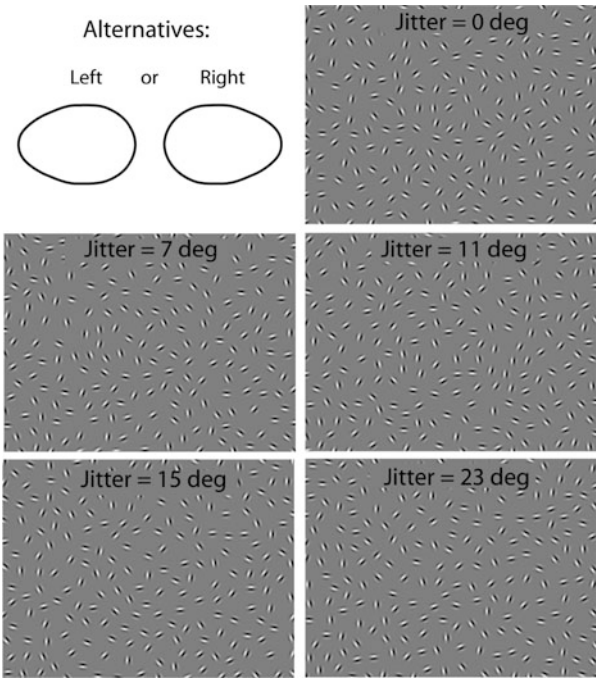

Fig. 5 Task and stimuli for JOVI experiments. Top left panel depicts the two basic shapes that subjects discriminated. Other panels show examples of stimuli from several of the conditions across the two versions of the task. The stimuli on the left are rightward pointing and those on the right are leftward pointing. Reprinted with permission from Silverstein et al. (2012)

deficits are limited to early visual cortex regions subserving the disordered eye, showing clear differences between amblyopic and fellow eyes (Kovacs et al. 2000; Chandna et al. 2001). FMRI data in humans (Altmann et al. 2003) and monkeys (Kourtzi et al. 2003) indicate a visual cortex basis for contour integration. We used a version of the JOVI for imaging with +/− 0°, 7–8°, 9–10°, 11–12°, and 13–14° trials. We also administered two types of catch trials (i.e., where no errors were expected) to ensure that all subjects were properly attending to and understanding the task. *Outline* catch trials consisted of 0° jitter stimuli with a black line tracing out the entire contour, obviating the need for integration; *no-background* catch trials also had 0°jitter, but these contained no-background noise elements (obviating the need for suppression of background noise). After covarying for number of catch trial errors, there were significant main effects of group, with overall worse performance in schizophrenia that did not vary as a function of jitter (Silverstein et al. 2015a, b). These results replicate prior studies (Kozma-Wiebe et al. 2006; Silverstein et al. 2009, 2012), in indicating that performance deficits in individuals with schizophrenia were relatively consistent across difficulty levels, with no differences between groups in early visual cortex (V1-V4). However, individuals with schizophrenia demonstrated increased (and presumably compensatory) activation across all jitter levels in the lateral occipital complex, an area critical for shape and object processing (Silverstein et al. 2015a, b; Keane et al. 2021). Individuals also demonstrated increased activation across all jitter levels in the superior parietal lobules, a region involved in binding of visual features and in distribution of visual-spatial attention.

Thus, the JOVI captures visual integration deficits in individuals with schizophrenia and reveals potential new regions of interest as biomarkers of deficits, including the lateral occipital complex and superior parietal lobules.

5 CNTRaCS Phase Two

After completing work on the tasks described above, the CNTRaCS consortium moved toward conducting similar work with new paradigms measuring additional features of the RdoCs Cognitive Systems, namely WM, plus constructs included as part of the RdoCs Positive Valence Systems. While task selection for the Positive Valence system domain had not gone through the same selection process as originally conducted for CNTRICS, CNTRaCS used the same principles in selecting measures to be examined for the Positive Valence Systems domain. Further, in the second phase of CNTRaCS, patient populations expanded to include individuals with Bipolar Disorder with Psychotic features to better understand transdiagnostic impairments within the psychosis spectrum, so at this time we changed the "S" in CNTRaCS to stand for Serious Mental Illness.

6 Working Memory

WM continues to be one of the most well-studied cognitive domains in schizophrenia (Lee and Park 2005; Forbes et al. 2009; Grot et al. 2014; Zhang et al. 2016; Liu et al. 2021) and is highlighted as part of the RdoCs Cognitive Systems domain. Importantly, there is a rich body of work examining both the psychological and neurobiological mechanisms that underlie WM (Goldman-Rakic 1995), with a general consensus that there are a number of different subcomponents of WM that may have dissociable neural mechanisms (Cowan 1988; Baddeley 2000). 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 s), serving as a temporary workspace (e.g., a "mental blackboard") supporting complex cognitive operations. 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.

Many studies demonstrate that individuals with schizophrenia exhibit deficits on a wide range of WM tasks and that these deficits are associated with functional impairments in neural circuits that support WM (Lee and Park 2005; Forbes et al. 2009; Grot et al. 2014; Zhang et al. 2016; Liu et al. 2021). Given the body of work on WM in schizophrenia, CNTRICS initially identified measures of two aspects of WM as ready for immediate translation for development and use in clinical trials in schizophrenia: (1) Goal Maintenance (see above); 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 described above, the first set of CNTRaCS projects focused on goal maintenance, and work by other investigators, see chapter "Working Memory in People with Schizophrenia" Luck and Gold, focused on interference control in relationship to attention, another RdoCs cognitive systems domain. However, as new data continued to emerge, CNTRaCS Phase Two turned to the critical issue of WM capacity, a construct highlighted at the first RdoC cognitive systems meeting and CNTRICs. WM capacity is sharply limited (typically 3–5 simple objects (Cowan 2010)). Individual differences in WM capacity are robustly correlated with a range of higher order cognitive abilities including IQ, fluid reasoning, language comprehension, and cognitive control (Brewin and Beaton 2002; Unsworth et al. 2009; Fukuda et al. 2010; Gold et al. 2010). Thus, pathological reductions in WM capacity should be expected to have widespread negative consequences. In the domain of WM capacity, Gold and Luck used change detection tasks in several experiments to show that individuals with schizophrenia demonstrate sizeable and replicable WM capacity impairments (Gold et al. 2002, 2006, 2010), typically manifest as a downward shift in a computed measure of capacity ("K"). Such K scores are substantially correlated with neuropsychological performance as indexed by the MATRICS total score ($N = 76$, $r = 0.52$). Although perceptual deficits might artifactually lead to the appearance of reduced capacity in many WM tasks (Haenschel et al. 2007; Dias et al. 2011), robust patient deficits can be observed in variants of this task when perceptual ability is factored out (Gold et al. 2010).

Visual change detection tasks provide a purer estimate of storage capacity than many traditional WM tests (Cowan 2010). Participants are shown a brief "sample array" (100–200 ms) containing N items (e.g., 5 color patches; see Fig. 6). After a short delay (~1,000 ms), subjects are shown a "test array" that is either identical to the sample or includes an item that has changed. Participants must indicate whether a change is detected. An ideal subject with a storage capacity of "K" items will be 100% correct when $N <= K$. As N increases above K, there is increasing probability that the changed item is not in memory, so accuracy declines. Capacity (K) can be robustly measured from task performance.

In the second set of CNTRaCS projects, we also used the *multiple change detection task, which was* developed to address two problems that are acute in animal paradigms (Gibson et al. 2011). First, subjects may have occasional lapses of attention, leading to random responding. Our previous CNTRaCS studies indicated that such lapses can dramatically impair the construct validity of a measure (Barch et al. 2012). Second, larger set sizes are more difficult and subjects may exert less effort as "N" increases. Both factors would artificially decrease the estimated capacity for a subject. To address these issues, the multiple change detection task keeps *N* constant at one value (e.g., 5 items), while varying unpredictably the number of items that change. Again, subjects simply report whether a change was

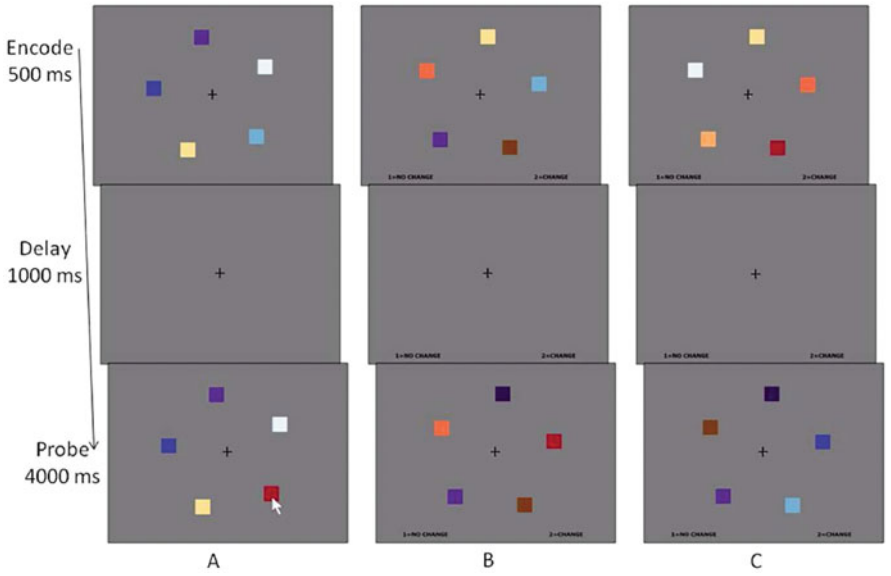

Fig. 6 Illustration (not to scale) of the Change Localization (**a**) and Multiple Change Detection tasks (**b**, **c**). In Change Localization a single item (circled) always differed between the encoding array and the test array. Panel (**b**) illustrates a trial where two items change from the encoding array to the test array. Panel (**c**) illustrates a "catch trial" from the Multiple Change Detection task where all five items changed on the test array. Reprinted with permission from Gold et al. (2018)

detected or not. Many of the trials are very easy (e.g., when all items change), keeping motivation high, and all trials seem equally easy to the subject. In addition, the subject should always be able to detect changes when all N items change, making it possible to measure lapse rates and factor them out from the WM capacity (K) measure. To minimize contributions of sensory imprecision, the changed color is always 180° (in color space) from the original color (see Fig. 6). Psychophysical studies show that color representations are sufficiently precise in both individuals and controls (Zhang and Luck 2008; Gold et al. 2010), and that there is a vanishingly small probability that an 180° color change would fail to be detected due to encoding imprecision. Thus, sensory precision reductions in individuals with schizophrenia cannot meaningfully distort capacity estimates. One consideration is that 7-10% of males have red-green color blindness, hence we also included a version using multidimensional objects where all dimensions change (and color changes are between wavelengths that can be discriminated by color-blind individuals). Multidimensional objects are stored just as easily as single-dimension objects in both controls (Luck and Vogel 1997) and individuals with schizophrenia (Gold et al. 2003) and multidimensional changes produce optimal performance levels (Awh et al. 2007). This design eliminates any effects of sensory imprecision on performance for anyone whose vision is good enough to qualify for participation. CNTRaCS compared this multiple change detection task to a change localization

task (two versions, one with just colored squares and one with color objects to parallel the multiple change detection task where one stimulus always changed each trial and the person had to use the cursor to identify which item changed (see Fig. 6 for example). For change localization we examined accuracy while for multiple change detection, we applied a mathematical modeling procedure to the accuracy scores for each trial type providing an estimate of WM capacity (K), the probability that the participant was paying attention on a given trial (A), and a guessing bias parameter (G).

Overall, healthy participants had higher capacity in both versions of the multiple change detection and change localization tasks compared to a combined patient group of schizophrenia, schizoaffective disorder, and bipolar disorder (Gold et al. 2018). However, capacity reduction was actually strongest in bipolar disorder and not significantly different in individuals with schizophrenia in the multiple change detection task. However all patient groups showed reductions in the "a" parameter as a measure of lapses of attention and higher guessing rates. The color square and color objects versions of each task yielded similar results, but anecdotally participants reported finding the color object versions of the task distracting and complicated. Thus, we moved the color square versions into a test-retest reliability study. We found excellent internal consistency for both the multiple change detection and change localization tasks, and moderate test-retest reliability for accuracy in individual conditions. However, test-retest reliability for the mathematically estimated capacity parameter was moderate and low for attention and guessing. Thus, accuracy measures on this task will be good for both group and individual difference/treatment studies, but the computationally derived parameters are currently better suited for group difference studies and will need enhancement for robust use in individual different and treatment studies.

7 Positive Valence Systems

The original CNTRICS process focused on constructs in the Cognitive Systems domain. However, both RDoCs and subsequent CNTRICS work focused on human/animal translational paradigms included a focus on the Positive Valence domain due, in part, to: a) a burgeoning affective neuroscience literature in human and animal systems revealing core neural systems that process and integrate reward and penalty signals, and translate these signals into value and/or utility estimates that can be used to drive action selection and planning and b) a growing literature suggesting that disruptions in components of the Positive Valence domain are associated with motivation and life function impairments in schizophrenia. Positive Valence domain includes a number of constructs, including hedonics (initial responsiveness to reward attainment), reinforcement learning (RL), and preference-based decision making. Within RL, distinctions were made between negative and positive RL, and RL with and without conscious perception. In subsequent meetings, reversal learning, or the

ability to update stimulus response contingencies, was identified as another key aspect of positive valence systems.

RL is thought to be mediated by the midbrain dopamine (DA) system projections to ventral and dorsal striatal regions of the basal ganglia (Berridge 2004; Schultz 2007). The degree to which these neurons respond to rewards depends on predictability. Unpredicted rewards induce DA neurons to fire strongly (positive prediction error). If a predicted reward does not occur, transient depression in DA neuron firing occurs (negative prediction error) (Schultz 1992, 2004, 2007; Schultz et al. 1993, 1997). Over time, DA neurons learn to fire in response to cues that predict reward, rather than to rewards themselves. In humans there is evidence from fMRI for activation of ventral and dorsal striatum to cues that predict reward (Knutson et al. 2000, 2001) as well as both positive and negative prediction error responses (McClure et al. 2003; Abler et al. 2006). These DA/striatal responses are captured by temporal difference models that learn about stimuli in the environment that predict rewards (Montague and Sejnowski 1994; Montague et al. 1996). These mechanisms are thought to underlie aspects of RL that may occur *without* conscious awareness (Dayan and Balleine 2002; Frank et al. 2004). While there are common mechanisms that may contribute to RL with and without conscious awareness for both positive (reward) and negative (loss or punishment) feedback, there are also dissociable mechanisms. For example, there is evidence for striatal cells that mediate "go" or reward based learning versus cells that mediate "no-go" or punishment based learning, with a hypothesized role for D1 receptors in go learning and D2 receptors in no-go learning (Frank et al. 2004; Frank and O'Reilly 2006; Hazy et al. 2007; Frank and Hutchison 2009). There is also growing evidence of a role for serotonin in negative RL (Evers et al. 2005; Crockett et al. 2009; Bari et al. 2010). Theories of RL postulate that *RL with conscious awareness* involves interactions between striatal learning systems and orbitofrontal cortex (OFC) (Schoenbaum and Roesch 2005; Frank and O'Reilly 2006). A number of theories suggest that the OFC supports the ability to represent value information, taking into account both the hedonic properties of a stimulus and the motivational state of the organism (e.g., value of juice when thirsty versus not) (Rolls et al. 1989), during the delay before the reward occurs (Roesch and Olson 2005; Rudebeck et al. 2006), different reward options available (e.g., juice vs wine after a hard day) (Padoa-Schioppa and Assad 2006; Padoa-Schioppa 2007), and changing contingencies associated with stimuli (a previously rewarded response is now punished) (Dias et al. 1996). Some researchers described the OFC as being involved in "working memory" for value, the ability to explicitly maintain, update, and integrate different sources of information about value (Frank and O'Reilly 2006; Wallis 2007). Human fMRI shows activation of OFC in conditions requiring value representations (O'Doherty et al. 2003; O'Doherty J 2007), including those in which response contingencies need to be updated, such as reversal learning (Cools et al. 2002, 2007; O'Doherty et al. 2003). Humans with OFC lesions also show reversal learning impairments (Fellows and Farah 2003, 2005; Hornak et al. 2004), consistent with numerous targeted animal OFC lesion studies (McAlonan and Brown 2003; Clarke et al. 2008; Man et al. 2009).

The literature on RL in schizophrenia is mixed, though distinctions between with and without conscious awareness and between positive and negative RL help shed light on these data. If one focuses on studies using paradigms engaging RL without conscious awareness, many studies suggest intact learning in schizophrenia. For example, intact learning of initial discriminations in reversal learning (Waltz et al. 2007) and ID-ED tasks (Elliott et al. 1995; Hutton et al. 1998; Joyce et al. 2002; Turner et al. 2004; Tyson et al. 2004; Jazbec et al. 2007; Ceaser et al. 2008), and intact learning *rates* on probabilistic learning tasks (Keri et al. 2000; Weickert et al. 2002, 2009; Beninger et al. 2003; Keri et al. 2005; Weiler et al. 2009) are repeatedly observed, with a few exceptions (Oades 1997; Pantelis et al. 1999; Foerde et al. 2008; Horan et al. 2008). Further, both Gold's (Heerey et al. 2008) and Barch's groups found evidence for intact positive RL in schizophrenia using the Pizzagalli bias learning task (Pizzagalli et al. 2005). In contrast, one finds more robust evidence for deficits in SCHIZOPHRENIA on explicit RL tasks that may engage OFC (Gold et al. 2008) as well as striatal mechanisms (Waltz et al. 2007, 2011; Morris et al. 2008; Koch et al. 2009; Strauss et al. 2011). This literature also suggests distinctions between learning from positive and negative feedback in individuals with schizophrenia, with a series of studies showing impaired positive RL ("Go" learning), but intact negative RL ("No-Go") (Waltz et al. 2007, 2011; Polgar et al. 2008; Strauss et al. 2011), though see Somlai et al. (2011) for exception. The literature also provides evidence for impaired reversal learning in schizophrenia (Pantelis et al. 1999; Jazbec et al. 2007; Waltz et al. 2007; Murray et al. 2008; Leeson et al. 2009; McKirdy et al. 2009; Weiler et al. 2009). Importantly, there is robust evidence that the magnitude of RL and reversal learning impairments in schizophrenia is correlated with severity of anhedonia/amotivation symptoms (Farkas et al. 2008; Murray et al. 2008; Polgar et al. 2008; Somlai et al. 2011; Strauss et al. 2011; Waltz et al. 2011), with some evidence that negative symptoms are specifically related to positive compared to negative RL (Polgar et al. 2008; Somlai et al. 2011). Hence, RL paradigms provide insight into potential neural mechanisms underlying deficient cognition in individuals with schizophrenia, with largely consistent findings highlight the importance of conscious vs. unconscious awareness, and the impact of positive vs. negative RL.

Reinforcement Learning Without Conscious Awareness. Relatively few tasks isolate RL without conscious awareness, as they frequently conflate both with and without awareness constructs (e.g., the Weather Prediction Task (Gluck et al. 2002)). Thus, CNTRaCS used a bias learning task to specifically isolate RL without conscious awareness, as participants are consistently unaware of reinforcement contingencies (Pizzagalli et al. 2005, 2007; Bogdan and Pizzagalli 2006, 2009; Bogdan et al. 2010). This task has an animal analogue that was recommended for further development in CNTRICs (Moore et al. 2013). Participants decide whether a briefly presented mouth on a face is either short or long. One type of correct response is reinforced at a higher rate than another. Signal detection indices assess accuracy (d-prime) and bias to respond with the more highly rewarded or more highly punished response type (beta). The original Pizzagalli task focused on *positive* feedback. CNTRaCS also developed a version that focuses on *negative* feedback.

The logic of this version is identical to the positive version, as one type of incorrect response is provided with feedback at a higher rate than the other type. Individuals also develop a bias about the response type that receives more feedback, which increases across blocks. CNTRaCS also developed multiple stimulus sets for these tasks, to allow for repeated testing. In both CNTRaCS studies of these tasks we found robust evidence that participants developed the expected bias about the more rewarded versus more punished stimulus. Like prior research, we found that RL without conscious awareness was intact in schizophrenia (as well as in bipolar disorder) (Barch et al. 2017; Pratt et al. 2021), though we found some evidence of increased reward bias associated with greater mania symptoms. A CNTRaCS test-retest reliability study found that performance on these RL tasks showed good internal consistency, but poor test-retest reliability, particularly for patient groups (Pratt et al. 2021). Thus, this task may be good for characterizing group differences in RL without conscious awareness, but is likely not as useful for individual difference or treatment studies.

Reinforcement Learning with Conscious Awareness. For RL with conscious awareness, CNTRaCS optimized a task paradigm developed by Pessiglione (Pessiglione et al. 2006) and Kim (Kim et al. 2006a, b). Participants are asked to learn which image in a pair of images is either more associated with winning (e.g., potential gains) or more associated with not losing (potential loses). Gold and colleagues (2012a, b) demonstrated that schizophrenia participants with high versus low negative symptoms are impaired learning from positive feedback, but do not differ in learning from negative feedback. As shown in Fig. 7a, on potential gain trials, if the correct item is selected, participants see an image of a nickel and the word "Win," whereas if the incorrect item is selected, they see "Not a winner, try again." On correct potential loss trials (Fig. 7b, participants see "Keep your money," whereas if the incorrect item is selected, they see a nickel with a red cross through it and the word "Lose." The correct response is reinforced on either 90% of trials (one condition) or 80% (another condition). Thus, there were a total of four types of trials: (1) Win/Not Win at 90/10 probability distribution; (2) Win/Not Win at 80/20 probability distribution; (3) Not Lose/Lose at 90/10 probability distribution; and (4) Not Lose/Lose at 80/10 probability distribution. To generate multiple parallel versions that could be used in longitudinal or treatment studies, we developed four different sets of stimuli. As dependent measures we compute both model based learning rates for achieving gains and avoiding losses (Gold et al. 2012a, b) and accuracy in the last block. Following training, a transfer test phase is presented. In these 72 trials, the original four training pairs are each presented four times, with novel pairings presented on 58 trials. For novel pairings, each trained item is presented with every other trained item. Of most interest were pairings that pitted stimuli that had experienced different types of reinforcement histories against each other (referred to as pairings). Participants were instructed to pick the item in the pair that they thought was "best" based on their earlier learning. No feedback was administered during this phase. Thus, this straightforward task provides a rich set of RL measures.

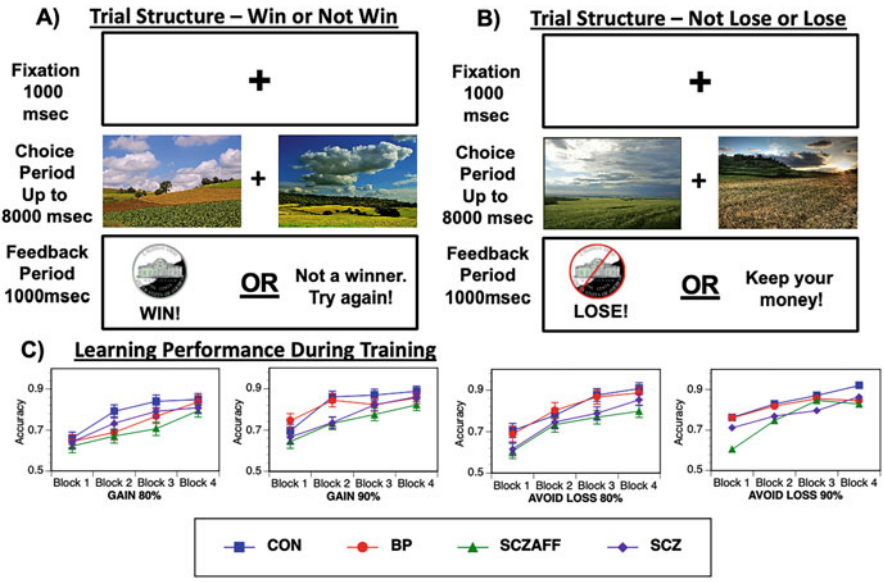

Fig. 7 Schematic and stimulus examples for the Explicit Probabilistic Incentive Learning Task (EPILT) for (**a**) obtaining reward; and (**b**) avoiding punishment, as well as Training Performance in the EPILT as a function of Diagnostic Group. Reprinted with permission from Barch et al. (2017)

As shown in Fig. 7c, and consistent with other work (Gold et al. 2012a, b; Abohamza et al. 2020), in two CNTRaCS studies, both individuals with schizophrenia and schizoaffective disorder performed significantly worse than controls in the learning phase (Barch et al. 2017; Pratt et al. 2021), and in one study individuals with bipolar also performed poorly (Pratt et al. 2021). In the transfer phase, all patient groups showed intact sensitivity to which stimuli were more associated with losing versus winning, but individuals with schizophrenia and schizoaffective disorder showed less sensitivity to the frequency of winning. Taken together, these data indicate some evidence of reduced sensitivity to frequent reward amongst patient groups. This finding is generally consistent with prior work (Gold et al. 2012a, b), who also found impaired sensitivity to the frequency of winning among individuals, but only among those with impairments in motivation. Importantly, worse performance on the explicit RL task was related to worse motivation and pleasure symptoms across all individuals and was also related to WM. Relationships between explicit RL learning and WM accounted for some of the diagnostic group differences, but did not explain relationships between explicit RL and motivation and pleasure symptoms. These findings suggest transdiagnostic relationships across the spectrum of psychotic disorders between motivation and pleasure impairments and RL with conscious awareness. Like the RL without conscious awareness tasks, internal consistency was strong for the training phase of explicit RL, though less so for the transfer phase (Pratt et al. 2021). Test-retest reliability was modest for the training phase and poor for the transfer phase (Pratt et al. 2021). Thus, the training/

learning measures of RL with conscious awareness will be useful for both group discrimination and individual difference/treatment studies, but not the transfer phase measures are likely most useful for group difference studies only.

Reversal Learning. CNTRaCS optimized Cools' paradigm previously used in human and animal studies (Clark et al. 2004), including fMRI (Cools et al. 2002, 2007; Funkiewiez et al. 2006; Robinson et al. 2010) and PET studies of dopaminergic and serotonergic influences on reversal learning (Evers et al. 2005; Cools et al. 2007; Clatworthy et al. 2009). It was recommended for further development during CNTRICs. Participants are presented with pairs of items and told that one stimulus from each pair is "correct," and that they have to figure out which one. They are told that no stimulus is correct all the time, and that the "correct" stimulus changes occasionally. The choice of one of the stimuli is positively reinforced 80% of the time (the other stimulus is reinforced 20%). Once participants reach an initial criterion, the contingencies are reversed. This type of task can also be conducted in rodents (Bari et al. 2010; Amitai et al. 2014; Milienne-Petiot et al. 2018), and results in consistent EEG biomarkers of performance (Cavanagh et al. 2021). Participants are required to detect the shift in reinforcement contingencies and learn to choose the stimulus now reinforced 80% of the time. If participants succeed in reaching criterion in this phase, they are considered to have successfully achieved a *reversal*. Gold has shown that individuals with schizophrenia learn the initial discrimination, but make fewer reversals and more errors before successful reversals (Waltz and Gold 2007). This task has excellent construct validity and elegant animal literature to support the involvement of striatal and OFC systems. However, the ability to interpret selective deficits in reversal is hampered by the fact that the initial discrimination stage is easier and has lower discriminating power. Thus, CNTRaCS developed a version in which the initial discrimination and reversal are better-matched psychometrically in controls, by reducing the difficulty of the reversal learning trials (90% rather than 80%), making the initial discrimination and reversal conditions better psychometrically matched in controls. Individuals with schizophrenia, schizoaffective disorder, and bipolar disorder were all impaired on both initial discrimination and reversal. Bayesian hidden Markov modeling (Rouder et al. 2009; Wagenmakers et al. 2017a, b) within a series of hierarchically nested models (Daw et al. 2011) revealed that all three groups made more errors due to a greater tendency to shift away from rewarded categories. Formal modeling showed a reduction in $\beta_{temperature}$, implicating a reduction in exploitation of known rewards, and allowed us to rule out two other hypotheses, namely that this behavior reflects deficits in belief states ($\delta_{transition}$) or attention lapses ($\lambda_{lapse\ rate}$). Thus, reversal learning tasks offer an opportunity to reveal positive RL deficits in patient populations, as seen in individuals with schizophrenia.

8 Future Directions of CNTRACS: Phase Three

As the field advances toward precision psychiatry, we need clinically informative measures with good psychometric properties that: (1) optimally differentiate individuals and controls, (2) capture variance in important symptom dimensions and functional outcomes, and (3) are sensitive to treatment effects. The CNTRaCS initiative has helped move the field from traditional neuropsychological measurement to cognitive-neuroscience-based approaches, including the development of imaging biomarkers, made freely available to the field and industry (http://cntracs.ucdavis.edu). Psychiatric research is now undergoing significant advances in a new subspecialty of computational psychiatry, complementing cognitive neuroscience constructs with an expanding paradigm of neurocomputational modeling. The scientific premise of this work is that the computations (i.e., algorithm-based transformations of information) performed by neural circuits can be estimated, and that these parameter estimates bridge the gap between neural circuit function, cognition, and behavior. Consequently, the ways in which pathophysiology generates psychopathology can be specified and tested using mathematical formalisms (Redish and Gordon 2016). Within this context, the CNTRaCS consortium modified its acronym again, such that the "C" now referred to Computational Neuroscience, allowed us to maintain continuity while growing our goal. Thus, the third phase of CNTRaCS aims to provide the field with a set of "vetted" tasks and associated computational models that meet the measurement standards needed for clinical research. We selected task + model combinations on the basis of four criteria: (1) a rich clinical literature suggesting relevance for a broad range of psychopathology; (2) the ability to quantify underlying processes that contribute to a broad range of tasks; (3) the ability to distinguish between specific deficits and non-specific or generalized deficits; and (4) when possible, paradigms for which neural measures can be used to provide biological validation of the model parameters. The first study of this third phase is ongoing, recruiting healthy controls, as well as individuals with schizophrenia, schizoaffective disorder, bipolar disorder with psychotic features, and major depression.

These criteria led us to focus on the domains of visual perception, WM, EM, reinforcement learning (RL), and effort-based decision making – functions that span much of the behavioral geography of the brain and which are part of the RDoC matrix (Insel et al. 2010; Morris and Cuthbert 2012; Cuthbert and Kozak 2013). Each of these domains has clear relevance to psychotic disorders and is also increasingly relevant to affective, substance use, and personality disorders. Whereas existing measures often treat each of these domains as monolithic constructs, the computational models we propose can disentangle multiple processes that underlie each domain, illuminating the neural basis of comorbidity and heterogeneity. For example, we expect that a significant proportion of impairments in visual perception, WM and EM in individuals with psychotic disorders will be accounted for by a single computational parameter reflecting the *precision* with which information is represented. Conversely, we predict that both psychotic and depressed individuals

will exhibit deficits in RL but will differ in the model parameters that are impaired, reflecting different pathways by which performance is disrupted.

To be concrete, consider the domain of visual perception and the computational parameter of *precision*, defined as the degree to which a neural representation consistently matches the properties of a particular stimulus. A more narrowly tuned neuron provides a more precise representation of orientation, making it easier to discriminate between similar line orientations. Behaviorally, schizophrenia individuals exhibit impaired precision in the form of broadened orientation tuning (Yoon et al. 2010; Rokem et al. 2011; Schallmo et al. 2013), hypothesized to reflect altered excitation/inhibition (E/I) balance (Krystal et al. 2017) and/or coarsening of representations to compensate for excessive neural noise (Silverstein et al. 2017). Because these alterations may impact neural function in schizophrenia at multiple levels of analysis (Krystal et al. 2017), reduced precision is hypothesized to contribute to aberrant representations across domains of cognition, including perception, memory, and belief formation (Javitt et al. 1997; Rokem et al. 2011; Schallmo et al. 2013; Krystal et al. 2017). Moreover, reduced precision contributes to both orientation discrimination deficits and impaired WM in schizophrenia (Rokem et al. 2011; Starc et al. 2017). These data are consistent with animal and human data showing that precision is a critical variable in orientation tuning (Edden et al. 2009; Katzner et al. 2011), in WM performance (van den Berg et al. 2012), and in hippocampally-mediated EM (Koen et al. 2017; Kolarik et al. 2018). Whereas these domains have historically been conceptualized as independent constructs, we are using tasks and models that isolate a precision parameter (a construct with significant links with functional outcome measures) (Green et al. 2012; Sheffield et al. 2014; Zaragoza Domingo et al. 2015; MacQueen and Memedovich 2017; Soni et al. 2017) across domains to determine the extent to which reduced precision may account for multiple aspects of cognitive pathology in psychotic (Park and Gooding 2014; Berna et al. 2016; Silverstein 2016) and affective disorders (Bubl et al. 2015; Bora 2018; Dillon and Pizzagalli 2018).

In many behavioral tasks, incorrect responses can arise either from imprecise neural coding or from lapses of attention. Indeed, a previous CNTRaCS study demonstrated that a putative perceptual deficit in schizophrenia individuals could be explained by attentional lapses (Barch et al. 2012). This premise underscores the need for the task-model combinations that provide independent estimates of precision and lapse rate for each participant. Lapses of attention often reflect failures of goal maintenance (Smeekens and Kane 2016; Kane et al. 2017), an aspect of cognitive control that has been shown to be specifically impaired in psychotic disorders and is associated with atypical activation and connectivity in the frontal-parietal attention network (Phillips et al. 2015). Importantly, we are also including EEG recordings in our ongoing CNTRaCS study to identify potential neural correlates of the computationally derived metrics, using cost-effective EEG/ERP methods that are feasible to use in larger-scale studies. For example, we are measuring pre-trial alpha-band oscillations, which are shown to predict lapses in attention (Erickson et al. 2016; Boudewyn and Carter 2018).

In addition to precision and lapsing, *capacity* (the number of items that can be simultaneously represented) is a key factor in the efficient performance of complex tasks. Like precision, WM capacity depends critically on E/I balance (Wei et al. 2012), and it also appears to depend on the balance of D1 and D2 receptor activity (Durstewitz and Seamans 2008). However, impaired performance on WM tasks may be due to poor precision, high lapse rate, or a true capacity deficit, and the computational modeling in CNTRaCS will separate each of these parameters for each subject. Using both behavioral and EEG (Erickson et al. 2016) methodology, we have shown that individuals across a spectrum of psychotic disorders – including bipolar disorder – exhibit separable deficits attributable to capacity limits and lapsing.

In addition to measures of "cold" cognition, CNTRaCS III includes task + model combinations examining abnormalities in motivation and goal-directed behavior relevant for affective and psychotic disorders. Specifically, we are studying reinforcement learning (RL) and effort valuation, two key constructs from the Positive Valence Systems in the RDoC matrix. We and others consistently found these constructs to relate to motivational symptoms in schizophrenia, bipolar disorder, and depression (Gold et al. 2012a, b, 2013; Barch et al. 2016, 2017). However, the unique contributions of multiple neural and cognitive systems that give rise to RL and effort valuation deficits differ across disorders in ways that cannot be detected without specialized tasks and models. For example, in RL, abnormalities may occur in the ability to signal *reward prediction errors* (RPEs). RPEs are events that are better or worse than expected and are linked to dopaminergic function (Schultz 2016). Altered RPEs can have marked motivational consequences across mental illnesses (Maia and Frank 2011, 2017). Alternatively, changes in RL could arise due to alterations in downstream targets of the RPEs (e.g., in striatum) and in updating of *value representations.* In effort-based decision making, changes in the willingness to invest effort can arise not only from an amplification of the cost of effort, but also from impairments in maintaining prospective reward *value representations* in WM. Reduced WM capacity can therefore lead to impaired performance in these tasks. As shown in Preliminary Data, our computational models demonstrate that the RL deficits widely observed in schizophrenia are secondary to reduced WM capacity rather than reflecting impairments in reward signaling and prediction errors (Collins et al. 2014, 2017), whereas the latter appears may be a more primary deficit in affective disorders (Zhang et al. 2013; Barch et al. 2016). Such a distinction has important implications for the development and assessments of new treatments. This type of insight is only achieved with optimized experimental designs accompanied by quantitative modeling. This approach also maps behavioral task parameters to EEG markers of RL, such as the well-validated Reward Positivity (Fromer et al. 2016; Heydari and Holroyd 2016) also seen in mice (Cavanagh et al. 2021), and newer decoding-based EEG indices of RL (Frank et al. 2015; Collins and Frank 2016).

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