Published in final edited form as:

J Abnorm Psychol. 2018 October ; 127(7): 695–709. doi:10.1037/abn0000369.

Effects of Reward on Spatial Working Memory in Schizophrenia

Youngsun T. Cho[1,2], **Norman H. Lam**[3], **Martina Starc**[4], **Nicole Santamauro**[1], **Aleksandar Savic**[5], **Caroline K. Diehl**[1], **Charles H. Schleifer**[1], **Flora Moujaes**[1,2], **Vinod H. Srihari**[1], **Grega Repovs**[4], **John D. Murray**[1,3], and **Alan Anticevic**[1,6,7,8,9]

[1]Department of Psychiatry, Yale University School of Medicine, 300 George Street, New Haven, CT 06511, USA

[2]Child Study Center, Yale University School of Medicine, 230 South Frontage Road, New Haven, CT 09520, USA

[3]Department of Physics, Yale University, 217 Prospect Street, New Haven, CT 06511

[4]Department of Psychology, University of Ljubljana, Ljubljana, Slovenia

[5]University Psychiatric Hospital Vrapce, University of Zagreb, Zagreb 10000, Croatia

[6]Abraham Ribicoff Research Facilities, Connecticut Mental Health Center, New Haven, CT 06519, USA

[7]Department of Psychology, Yale University, 2 Hillhouse Avenue, CT 06520, USA

[8]Interdepartmental Neuroscience Program, Yale University, New Haven, CT 06520, USA

[9]NIAAA Center for Translational Neuroscience of Alcoholism, New Haven, CT 06519, USA

Abstract

Reward processing and cognition are disrupted in schizophrenia (SCZ), yet how these processes interface is unknown. In SCZ, deficits in reward representation may affect motivated, goal-directed behaviors. To test this, we examined the effects of monetary reward on spatial working memory (WM) performance in patients with SCZ. To capture complimentary effects, we tested biophysically-grounded computational models of neuropharmacologic manipulations onto a canonical fronto-parietal association cortical microcircuit capable of WM computations. Patients with SCZ (n=33) and healthy control subjects (HCS) (n=32) performed a spatial WM task with two reward manipulations: reward cues presented prior to each trial, or contextually prior to a block of trials. WM performance was compared to cortical circuit models of WM subjected to feed-forward glutamatergic excitation, feed-forward GABAergic inhibition or recurrent modulation strengthening local connections. Results demonstrated that both groups improved WM performance to reward cues presented prior to each trial (HCS d=−0.62; SCZ d=−1.0), with percent improvement correlating with baseline WM performance (r=0.472, p<0.001). However,

CORRESPONDENCE: Alan Anticevic, alan.anticevic@yale.edu, Department of Psychiatry, Yale University.

General Scientific Summary: Patients with schizophrenia experience decreased motivation and have cognitive deficits. This work suggests that decreased motivation may be related to difficulty keeping future rewards in mind over longer periods of time.

DISCLOSURES:

Dr. Anticevic consults and is a member of the SAB for BlackThorn Therapeutics. Dr. Murray consults for BlackThorn Therapeutics. All other authors report no biomedical financial interests or other potential conflicts of interest.

rewards presented contextually before a block of trials did not improve WM performance in patients with SCZ (d=0.01). Modeling simulations achieved improved WM precision through strengthened local connections via neuromodulation, or feed-forward inhibition. Taken together, this work demonstrates that patients with SCZ can improve WM performance to short-term, but not longer-term rewards—thus motivated behaviors may be limited by strength of reward representation, and, additionally, baseline WM performance. A potential mechanism for transiently improved WM performance may be strengthening of local fronto-parietal microcircuit connections via neuromodulation or feed-forward inhibitory drive.

Keywords

schizophrenia; reward; cognition; working memory; computational modeling

INTRODUCTION

Schizophrenia is marked by a decrease in motivated, goal-directed behaviors, as well as in cognition (Foussias et al., 2011; Lewis & Lieberman, 2000; Schlosser et al., 2014). Typically organized under ‘negative’ and ‘cognitive’ domains, these symptoms are thought to arise, in part, from impairments in reward processing and core cognitive processes, respectively (Fioravanti, Bianchi, & Cinti, 2012; Reddy, Horan, & Green, 2016). Both negative and cognitive symptoms predict level of functioning, with more severe symptoms leading to worse functioning (Green, 1996; Milev, Ho, Arndt, & Andreasen, 2005), yet the way in which they interface remains unknown (Harvey, Koren, Reichenberg, & Bowie, 2006). Therefore, understanding how reward processing and cognition interface may be important for understanding symptomatology and designing future treatments.

Reward representation, i.e., the keeping in mind of potential rewards, is an elemental way in which rewards exert motivational influence (Berridge, 2012). Impaired reward representation has been hypothesized in SCZ, (Barch & Dowd, 2010; Gold, Waltz, Prentice, Morris, & Heerey, 2008) and is supported by decreased neural responses during reward anticipation, and after emotional stimuli disappear in patients with SCZ (Juckel et al., 2006; Nielsen, Rostrup, Wulff, Bak, Broberg, et al., 2012; Nielsen, Rostrup, Wulff, Bak, Lublin, et al., 2012; Radua et al., 2015; Ursu et al., 2011). This is further supported by a separately noted deficit in manipulating contextual information in patients with SCZ (Barch et al., 2001; Barch, Carter, MacDonald, Braver, & Cohen, 2003). Together, these works have linked the motivational capacity of rewards with cognitive capacity rather than affective influence (Burbridge & Barch, 2007; Heerey, Bell-Warren, & Gold, 2008; Heerey, Matveeva, & Gold, 2011), as reward consumption has largely been shown to be intact in SCZ (Berenbaum & Oltmanns, 1992; Blanchard, Bellack, & Mueser, 1994; Dowd & Barch, 2010; Gard, Kring, Gard, Horan, & Green, 2007; Heerey & Gold, 2007; Kring & Neale, 1996; Ursu et al., 2011).

One way to examine the reward-cognition interface is to examine the effect of rewards on core cognitive processes, such as working memory (WM). In healthy control subjects, (HCS), rewards have been shown to improve cognitive performance, including in tasks

requiring cognitive control (Chiew & Braver, 2014; Dixon & Christoff, 2012), rule-based contextual cognition (Locke & Braver, 2008; Rowe, Eckstein, Braver, & Owen, 2008), and verbal and visual working memory (WM) (Jimura, Locke, & Braver, 2010; Krawczyk, Gazzaley, & D'Esposito, 2007). Functional magnetic resonance imaging studies (fMRI) in HCS, and neurophysiologic recordings in non-human primates have suggested that prefrontal cortical regions integrate reward and cognitive processes (Jimura et al., 2010; Kennerley & Wallis, 2009; Krawczyk et al., 2007; Pochon et al., 2002; Taylor et al., 2004; Watanabe, Hikosaka, Sakagami, & Shirakawa, 2002), raising questions of how neuronal firing translates to behavior. Limited experimentation done in patients with SCZ has shown that monetary rewards improve reaction time in an n-back task (Hager et al., 2015), and performance in the Wisconsin Card Sorting Task (Summerfelt et al., 1991), but not accuracy in verbal WM or n-back testing (Hager et al., 2015; Thornton et al., 2007). None of these has studies explicitly tested how the strength of reward representation affects cognitive performance.

Furthermore, despite the large body of work examining spatial WM and affective processes at the neuronal level in non-human primates, and at the behavioral level in human subjects, there have been limited attempts to bridge the two findings. Computational, theory-driven models can be used to link measured human behavioral findings with computationally-derived neuronal mechanisms to create mechanistic hypotheses (Huys, Maia, & Frank, 2016). Such models have the advantage of highlighting molecular, synaptic or neuronal-level mechanisms that continue to be difficult to measure in human subjects at this time. When applied to clinical questions, the implications for steering testable treatment targets, and differential diagnoses becomes a key advantage of these theory-driven models (Anticevic & Murray, 2017; Huys et al., 2016; Wang & Krystal, 2014). Therefore, the utility of these models lies in generating hypotheses of the neuronal mechanisms underlying more readily measured phenomena, such as behavior.

Here, we jointly present behavioral findings and computational, theory-driven modeling of a fronto-parietal association cortical circuit model of WM from a task integrating monetary reward and spatial WM carried out in patients with SCZ and HCS. The latter experiment was a priori designed to hypothesize possible microcircuit mechanisms that may contribute to changes in WM performance in response to rewards. To characterize the influence of reward on WM performance, two separate reward manipulations were employed. First, the possibility for reward was cued prior to each WM trial. Second, rewards were contextually cued prior to a block of WM trials. In this way, we tested the strength of reward representation by separately examining the trial-by-trial versus 'contextual' longer-term influence of rewards on WM performance. We used a well-validated spatial WM task translated from non-human primate experiments (Arnsten & Goldman-Rakic, 1998; Funahashi, Bruce, & Goldman-Rakic, 1989; Goldman-Rakic, 1999) and frequently used in animal and pharmacologic studies (Anticevic et al., 2012; Arnsten, Cai, Murphy, & Goldman-Rakic, 1994; Driesen et al., 2013; Funahashi et al., 1989; Vijayraghavan, Wang, Birnbaum, Williams, & Arnsten, 2007), to allow for adequate translation. In particular, non-human primate studies of neuronal firing during WM manipulations have facilitated the development of biophysically plausible, theory-driven computational models (Compte, Brunel, Goldman-Rakic, & Wang, 2000; Deco & Rolls, 2003; Murray et al., 2014). Such

models instantiate cortical microcircuit architecture capable of WM computations, and can accommodate pharmacologic simulations to generate testable hypotheses for human experimental studies (Murray et al., 2014), thus bridging human behavioral responses with neuronal firing. Collectively, the aims of this study were: 1. To test how reward cues (trial-by-trial vs. contextual manner) affects WM performance in SCZ relative to HCS; 2. To computationally characterize potential neuropharmacologic mechanisms underlying reward effects on WM performance in order to generate testable neural predictions of obtained effects. We first describe findings from our behavioral experiment, followed by our computational simulations to hypothesize neuronal mechanisms for our behavioral results.

METHODS

Subjects.

Subjects were recruited from outpatient psychiatry clinics at Yale University and Connecticut Mental Health Center (CMHC), and from the general community through advertisement. Patients with SCZ were independently diagnosed by two clinicians using the Structured Clinical Interview (SCID) for DSM-IV (First, Spitzer, Gibbon, & Williams, 2002). Patients met DSM-IV diagnoses for SCZ, or schizoaffective disorder, but no other Axis I diagnoses, at the time of diagnostic interview. History of nicotine or alcohol use was allowed, though not current alcohol/drug abuse/dependence, and proximal use of substances was not explicitly controlled for. HCS had no current, or lifetime history of, Axis I disorders in themselves or first-degree relatives, ascertained by interviews by two master's level or higher clinicians examining family membership and history of needing mental health care or having emotional disturbances. Exclusion criteria for all included a history of neurological conditions, contraindications to tolerating MRI, color blindness, and major medical comorbidities. 32 HCS and 33 patients with SCZ composed the final, age-matched sample (Table 1). All protocols were approved by the Institutional Review Board of Yale University (HIC# 1111009332).

Clinical Assessments and Medications.

The Scale for Assessment of Positive and Negative Symptoms (SAPS/SANS) (N. Andreasen & Grove, 1986) and the Positive and Negative Syndrome Scale (PANSS) (Kay, Fiszbein, & Opler, 1987) were used to quantify symptom severity. Clinical interviews and rating scales were conducted by two master's level or higher clinicians with expertise in schizophrenia and associated scales. The same rater conducted the SAPS/SANS or PANSS. As each of these scales scores different items, particularly with respect to the domain of negative symptoms, both were collected (Kumari, 2017; Marder & Galderisi, 2017; van Erp et al., 2014). Prescribed antipsychotics were converted to chlorpromazine (CPZ) equivalents (N. C. Andreasen, Pressler, Nopoulos, Miller, & Ho, 2010).

Working Memory Task.

Across trials, after brief fixation, participants encoded the spatial position of a colored circle (Figure 1, target) presented on-screen for 1.4 seconds. Target presentation was in one of 20 possible positions randomly presented throughout the task. Following target disappearance, participants maintained the initial target location, while centrally fixating (delay period, 10

seconds). Finally, participants used a high-resolution joystick to position a gray circle (probe) to the remembered initial target location. The possibility for reward based on WM performance was manipulated throughout the task.

Each subject completed 160 trials (Figure 1). The task began with 5 practice WM trials in order to familiarize subjects with the task and equipment. Following this, subjects performed a block of 15 WM trials (i.e. neutral WM trials without incentives). The performance in these trials was collected in order to achieve a 'baseline' performance of our task that was used to calibrate the reward sensitivity, and therefore difficulty in obtaining reward, for each individual. Unbeknownst to the individual, the performance of these 15 trials was immediately sorted from 1–15 (best to worst) using previously written code in E-Prime software. For each individual, regardless of group, the highest reward was given (3 points, represented as $ $ $ during feedback) if performance in the rewarded trial fell within the top 20% of their performances of the 15 originally sorted WM trials. The next highest reward (2 points, represented as $ $) was given if performance in the rewarded trial fell within the top 20–33% of the performances from the sorted WM trials. The final reward tier (1 point, represented as $) was given if performance in the rewarded trial fell within the top 33–50% of trials. At the end of the task, the total number of points was summed and multiplied by 0.066, and this amount was paid in dollars to the subject. Both groups won similar amounts (HCS=$10.54 +/− 1.27; SCZ=$10.48 +/− 1.39; ($t(64)=0.18$, $p>0.05$), suggesting that the individual-specific calibration was successful. Following the 15 WM trials for calibrating individual reward sensitivity, subjects performed three blocks of 40 trials each (12 minute blocks), with 3 trial types randomized across blocks. 30 trials were WM trials that involved no reward (neutral, red target), and 30 trials were WM trials that cued the potential for reward based on task performance (trial reward, green target). Color associations were explained prior to each block. During these cued reward trials, feedback communicating the number of points won was given (see above for description).

To control for differences in basic motor performance, 60 motor trials that did not require WM were randomly interspersed. Motor trials did not require maintenance—instead the target was continuously presented during the putative delay period. This meant the target location was continuously presented and disappeared just before the subject moved the joystick.

The task finished with a block of 20 WM trials (context reward, 6 minute block) prior to which subjects were informed that they could win money across the next set of trials, but would not receive further reminders of this. This design required the subject to maintain the rewarding context throughout the block, and tested if contextually presented rewards bias WM accuracy differently than trial-by-trial reward cues. Here, the targets were red, in order to focus on the manipulation of the subject instruction to maintain the rewarding context throughout the block. Specifically, green was not used in this manipulation in order to avoid the trial-by-trial cues that were associated with the earlier manipulation. While money could be won, no feedback was given after each trial. Given the relatively fewer number of context reward trials, analyses were re-run with 20 randomly sampled trials from other conditions in order to match context trials. The significance of all interactions, main-effects and contrasts were unchanged with these sampled trials.

Data Collection and Analysis.

The task was programmed using E-Prime 2.0 software (Psychology Software Tools, Pittsburgh, PA), and run on a Dell laptop computer with an LCD screen (1280 × 1024 pixel resolution). A high-precision joystick was used to manipulate the probe location. All data was collected with E-prime 2.0 software (Psychology Software Tools, Pittsburgh, PA).

WM performance was quantified using the Euclidean distance in pixels measured between initial target location and probe placement. Trials reflecting inadequate performance/effort (based on probe manipulation <1/3 of the radius of the ring of target presentation and >90º from the initial target presentation) were eliminated (<1% of all trials). Based on *a priori* hypotheses, the following questions were examined using linear mixed models and restricted maximum likelihood estimation (Type III Wald F tests with Kenward-Roger degrees of freedom): 1) Group differences in baseline spatial working memory performance, with motor performance as a regressor, group as a fixed factor, and subject as a random effect; 2.) Group differences in trial-by-trial rewarded WM performance (*Reward* (trial reward vs. neutral) x *Group*), with motor performance as a regressor, group and reward as fixed factors, and subject as a random effect; 3) Group differences in contextually rewarded WM performance (*Context* (context reward vs. trial reward vs. neutral) x *Group*), with motor performance as a regressor, group and context as fixed factors, and subject as a random effect. We conducted an additional exploratory model based on our findings, and examined group differences in WM performance in the first quarter of the Context Reward block, and in the final quarter of the Context Reward block, in order to further understand the effects of Context Reward. This model had motor as a regressor, group and Trial-Time (first 5 trials vs last 5 trials) as a fixed factor, and subject as a random effect. Analyses included motor performance as a regressor, given that t-tests demonstrated significant group differences in baseline motor performance. Post–hoc tests were done within group, as opposed to between-group, because of the consistently poorer performance of patients with SCZ, compared to HCS, across all conditions. Post-hoc tests and effect sizes were reported using adjusted means, and independent tests were Bonferonni corrected. Analysis of task performance was conducted in the R statistical computing environment (http://www.r-project.org).

Computational Modeling.

Full details of the original computational model implementation and architecture were previously reported (Murray et al., 2014). Briefly, we implemented a well-validated, biophysically-based model of an association cortical circuit (Carter & Wang, 2007; Compte et al., 2000) that outputted spatial WM performance through stimulus-selective, persistent neural activity. This model simulated a local cortical microcircuit containing thousands of spiking excitatory (E) pyramidal cells, individually tuned to angular location (Arnsten, 2011), and untuned inhibitory (I) interneurons. Recurrent synapses between excitatory pyramidal neurons and inhibitory interneurons were modeled with NMDA and GABA receptors, respectively. These recurrent excitatory and inhibitory connections allowed for manipulation to shift E/I balance, and to create a ‘disinhibited’ model that simulated the hypothesized NMDA receptor hypofunction on interneurons in SCZ (Anticevic et al., 2012; Belforte et al., 2010; Krystal et al., 2003; Murray et al., 2014). Stimulus input was a constant current with a Gaussian profile applied to a spontaneous state network for one second, and

meant to induce spatial position. This current was then maintained for 10 seconds to match task presentation (delay period) and induce WM representation. Injection of current transiently excited the subset of E-cells tuned to that specific location, and led to a persistent, bell-shaped activity pattern (bump attractor) that was consistent with prior reports of continuous pyramidal neuron firing during WM maintenance (Funahashi et al., 1989). The peak position of the WM activity pattern (slightly drifted due to stochastic background input) was recorded within a 100 ms window. Behavioral report location was decoded from neural WM activity pattern using the population vector approach. Time-dependent decay of WM precision was obtained by computing the across-trial variability of the decoded location as a function of delay duration.

With this base model, we tested three candidate modulations that could be engaged by reward-related, top-down signals to affect WM precision (i.e. the accuracy in positional representation in the microcircuit model). The first modulation was a positive scaling of the strengths of all local recurrent synaptic conductances, irrespective of excitatory or inhibitory status. This allowed for the potential capture of a neuromodulator influence (such as dopamine) (Brunel & Wang, 2001; Compte et al., 2000). For this neuromodulatory model, excitatory NMDA receptor and inhibitory GABA receptor conductances were scaled by equal factors, as previously modeled (Brunel & Wang, 2001); here, the qualitative model effects (i.e., changes in WM precision and mean firing rate) were robust within a 0.5—2 range for NMDA/GABA proportionality. Our second manipulation was to induce increased feed-forward, Poisson background input to I-cells, mediated by glutamatergic NMDA receptors, effectively increasing inhibition. The third was increased feed-forward background input to E-cells, also glutamatergically mediated, however, effectively increasing excitation. The two feed-forward modulations potentially captured the effect of an external glutamatergic input, such as could be activated by a reward signal. All modulations were applied at stimulus onset. Simulation code is available from the authors upon request.

RESULTS

Demographics.

Groups differed in racial composition (X-squared = 8.54, $p < 0.05$), and father's years of education ($t(64) = 2.39$, $p < 0.05$), but not maternal education or general parental socioeconomic status. Paternal education was not significantly correlated with WM performances for both groups, and therefore not included as a covariate. As per previously known deficits in SCZ, groups differed in participant education achieved, WRAT-3, IQ Verbal and Matrix, all PANNS subscores, and mean SAPS and SANS scores ($p < 0.001$ for all) (Table 1). Given expected group differences, these variables were not co-varied for.

Spatial WM and Motor Performance.

Patients with SCZ demonstrated significantly worse motor performance, when compared to HCS ($t(52.4) = -3.4$, $p < 0.005$). Given this group difference, as well as significant correlations between motor performance and WM performance for both groups (SCZ=0.741, $p < 0.001$; HCS=0.795, $p < 0.001$), motor performance was included as a regressor in subsequent

analyses. Using motor performance as a regressor, group as a fixed factor, and subject as a random effect, analysis with linear mixed modeling demonstrated significant group differences in spatial WM performance ($F(1,61.72) = 4.87$, $p<0.05$), with patients with SCZ demonstrating worse WM performance, than HCS (Figure 2A, B).

Effect of Reward on WM Performance.

A linear mixed model to examine the *Reward* (trial reward vs. neutral) x *Group* interaction was tested to see if presenting the possibility for reward before each WM trial affected performance. Results revealed a significant interaction ($F(1, 2830.75)=4.51$, $p<0.05$), and a significant main effect of Reward ($F(1,2831.15)=81.19$, $p<0.001$). The main effect of group trended towards significance ($F(1, 64.91)=3.93$, $p=0.052$). Each group demonstrated improved WM performance for rewarded trials, compared to neutral trials (adjusted SCZ: $t(126)=-5.74$, $p<0.001$, Cohen's $d=-1.0$(CI:(−1.37,−0.63))); HCS: $t(126)=-3.48$, $p<0.005$, Cohen's $d=-0.62$ (CI:(−0.91,−0.32))) (Figure 2A). Across trial types, the SCZ group exhibited worse WM performance, compared to HCS (adjusted $t(62)=-2.24$, $p<0.05$, Figure 2A, B).

Effect of Contextually Presented Rewards on WM Performance.

There was a significant interaction of *Context* (context reward vs. trial reward vs. neutral) *x Group* ($F(2,4100.9)=5.10$, $p<0.01$), as well as significant main effect of Context factor ($F(2,4101)=42.31$, $p<0.001$) and a significant main effect of Group ($F(1,63.2)=5.22$), $p<0.05$). Both SCZ and HCS exhibited significantly better performance in trials with trial-by-trial reward cues vs. neutral trials (adjusted SCZ: $t(126)=-5.74$, $p<0.001$, Cohen's $d=-1.0$(CI:(−1.37,−0.63))); HCS: $t(126)=-3.48$, $p<0.005$, Cohen's $d=-0.62$ (CI:(−0.91,−0.32))). Patients with SCZ also demonstrated significantly better WM performance for trial-by-trial rewards than contextual rewards (adjusted SCZ: $t(62)=-5.81$, $p<0.001$, Cohen's $d=-1.01$ (CI:(−1.38,−0.64))), while HCS demonstrated similarity between the trial-by-trial and contextual reward conditions (though with trend towards significance) (adjusted HCS: $t(126)=-2.16$, $p=0.083$, Cohen's $d=-0.38$ (CI:(−0.66,−0.1))) (Figure 3A, C). Patients with SCZ exhibited no performance differences between contextually rewarded, and neutral, WM trials, with a nearly null effect size (adjusted $t(126)=0.070$, $p>0.05$, Cohen's $d=0.01$ (CI:(−0.33, 0.36))) (Figure 3B). HCS, while not demonstrating statistically significant improvement, exhibited a modest effect size (adjusted $t(126)=-1.32$, $p>0.05$, Cohen's $d=-0.23$ (CI:(−0.56, 0.09))) (Figure 3B). We further explored this effect by examining WM performance in the first quarter of the Context Reward block (five trials), and final quarter of the Context Reward block (five trials), in order to understand the changes in performance over the course of the block. There was a significant *Group (SCZ vs. HCS) x Trial-time (first-five vs. final-five*) interaction, suggesting that the groups performed differently in the first five trials, as compared to the final five trials ($F(1,574.56)=5.97$, $p<0.05$). The SCZ group had significantly worse performance in the final five context trials, as compared to the first five context trials ($t(32)=2.21$, $p<0.05$). By contrast, there was no significant difference in the performance of the HCS group when comparing the first five with the last five Context trials ($t(1,31)=-0.656$, $p>0.05$) (see Supplemental Figures 1 and 2).

Clinical Correlates.

To test if clinical measures were associated with the influence of rewards on WM performance, correlations of clinical measures with percent improvement of WM in rewarded trials (((WM performance in neutral trials – WM performance in rewarded trials)/WM performance in neutral trials)*100) were examined in the SCZ group. There were no significant correlations of percent improvement of WM in either type of rewarded trial with CPZ equivalents. Given that our task probed reward-processing, we were particularly interested to see if rewarded WM performance was correlated with negative symptoms. There were no significant correlations of percent improvement of WM in either type of rewarded trial with PANNS Negative scores, GSANS Mean scores, the Avolition subscore of the GSANS or the Asocial/Anhedonia subscore of the GSANS (all $p>0.05$).

Correlation of Baseline WM with Rewarded WM.

We examined linear correlations to test if baseline WM performance (neutral trials) predicted improvement in response to rewards. Motor performance was controlled for with partial correlation analyses. There were no group differences in correlations between baseline WM and percent improvement in either rewarded trials or contextually rewarded trials, and therefore relationships were examined across all subjects (Fisher's r-z transform, $p>0.05$ for both). Results revealed a significant correlation between baseline spatial WM performance and percent improvement in trial-by-trial rewarded WM trials ($r=0.472$, $p<0.001$, Figure 4). The same analysis for percent improvement in contextually rewarded WM trials was not significant ($p>0.05$). Because any form of WM capacity may impact rewarded WM performance, we examined the effects of digit span performance, baseline spatial WM performance, and motor performance on rewarded WM performance using multiple regression. For percent WM improvement to trial-by-trial rewards, results revealed significant relationships for motor performance ($B=-1.105 +/- 0.300$, $p<0.01$), and baseline spatial WM ($B = 0.540 +/- 0.161$, $p<0.05$), but not digit span performance ($p>0.05$). Examination of percent WM improvement to contextual rewards was non-significant (all $p>0.05$).

Eye Movements During the Task.

To better understand task adherence, and test whether alternative strategies were used during task performance, we conducted a follow-up study. We collected and analyzed an independent dataset of patients with SCZ and HCS who performed our task with eye-tracking. In brief, our analysis of eye-tracking conducted in this independent sample demonstrated no differences between groups, and limited differences between task conditions in fixation at the center or the previously presented target location (see **Supplemental Materials**). Furthermore, subjects spent only a tiny percentage of time (0.66%) fixating at the remembered target location during the delay period, and there were no significant correlations between duration of fixation on the target location and accuracy (**Supplemental Materials**). Taken together, our analysis suggested adherence to the task, and a limited effect of target fixation during the delay period on spatial WM performance.

Computational Modeling of Modulated WM Precision.

To investigate potential synaptic and pharmacologic mechanisms underlying the improvement of WM precision by reward signals, we studied a previously developed computational model of spatial WM grounded in cortical neurophysiology (Figure 5A) (Murray et al., 2014). In both a 'control' and 'disinhibited' base model meant to simulate HCS and SCZ, respectively, we characterized the impact of three candidate modulations on WM precision and neural activity (Figure 5B): a positive scaling of recurrent synaptic strengths, previously used to model synaptic effects of neuromodulators such as dopamine (Brunel & Wang, 2001; Compte et al., 2000); and increased non-specific glutamatergic drive, either to inhibitory interneurons or excitatory pyramidal neurons. Echoing the similarity of behavioral results for the trial-by-trial reward condition, we found that the possible mechanisms for improved WM precision were the same for both groups. Specifically, recurrent scaling and feed-forward drive to inhibitory interneurons demonstrated improved WM precision in both the 'control' and 'disinhibited' models, though the 'disinhibited' model continued to demonstrate overall worse precision (Figure 5C-E). In contrast, feed-forward drive to pyramidal excitatory neurons degraded WM precision—a less likely mechanism for improving WM precision (Figure 5C-E). Interestingly, WM activity appeared stable under a wide range of recurrent scaling modulations, while feed-forward drive to inhibitory interneurons increased beyond a few percent destabilized WM maintenance (Figure 5D). Separate effects on firing rates were also noted, as recurrent scaling led to increased firing rates, and feed-forward drive to inhibitory interneurons led to decreased firing rates during WM (Figure 5F-G). Together, these three modulations produced dissociable and testable hypotheses linking spatial WM precision with neuropharmacological activity.

DISCUSSION

Understanding the effects of rewards on cognitive performance remains critical for understanding symptomatology and treatment targets in SCZ. This work examined the influence of rewards on spatial WM performance by presenting the possibility for reward in two different ways: prior to each WM trial, or contextually across a block of WM trials. Via this manipulation we dissociated specific reward-cognition interactions to test which aspects were intact, or disrupted, in SCZ. In general, patients with SCZ demonstrated increased WM performance in response to short-term, but not longer-term, rewards. Results showed that patients with SCZ improved spatial WM performance to trial-by-trial rewards when compared to both contextually rewarded and neutral WM trials. In contrast, the trial-by-trial rewarded WM performance in HCS was a significant improvement only in comparison to neutral WM trials. For both groups, improved WM performance in response to trial-by-trial rewards correlated with baseline spatial WM capacity and motor performance, suggesting key factors influencing spatial WM improvement in response to rewards. To shed light on potential neural mechanisms, we examined *in silico* neuropharmacologic mechanisms that could bias spatial WM precision in a computational modeling simulation. Based on these simulations, improved WM precision, as behaviorally measured in the trial reward conditions, may result from either recurrent scaling of synaptic strengths or increased feed-forward inhibition in fronto-parietal WM circuits.

Rewards Presented in a Trial-By-Trial Manner Boost WM Performance in HCS and SCZ.

Both patients with SCZ and HCS significantly improved spatial WM performance when the possibility for reward was explicitly cued before each trial. Effect sizes suggested that patients with SCZ and HCS have comparable ability to be motivated by short-term rewards. Importantly, the baseline disruption in cognitive processing noted in our study and others (Heinrichs & Zakzanis, 1998; Van Snellenberg, Torres, & Thornton, 2006) did not preclude improvement. Instead, baseline cognition predicted percent improvement on rewarded trials, and is in line with prior studies linking cognitive impairments with motivational deficits (Heerey et al., 2008; Heerey et al., 2011). We also noted strong correlations between motor performance, and baseline spatial WM performance for each group that likely reflected the importance of motor control in expressing WM representation in this joystick-driven task. Despite these strong correlations, between 37–45% of the variance in baseline spatial WM performance remained unaccounted for, and likely corresponded to other facets including, but not limited to, attention, representation and encoding, as is consistent with deficits noted in patients with SCZ (meta-analyses: (Forbes, Carrick, McIntosh, & Lawrie, 2009; Lee & Park, 2005)).

Prior studies in patients with SCZ have reported no effect of monetary reward on either verbal or n-back WM accuracy (Hager et al., 2015; Thornton et al., 2007), though one documented faster reaction times (Hager et al., 2015). Our results therefore extend prior findings in both patients with SCZ and HCS in several ways. First, we used a spatial WM task (rather than n-back or verbal), which provided a continuous assay of WM precision translatable to animal and computational work. Second, we found improved WM accuracy, as opposed to faster reaction times (often reported because performance accuracy is at ceiling (Beck, Locke, Savine, Jimura, & Braver, 2010; Hager et al., 2015; Jimura et al., 2010). Third, we calibrated the likelihood of reward in a subject-specific way based on individual WM performance, circumventing issues of ceiling/floor performance effects, and generalized performance deficits. Even in HCS, only one study has shown improved performance (rather than reaction time), using higher-loads of a verbal n-back (up to 4-back) under rewarded conditions (Thornton et al., 2007). It is possible that the neural systems recruited for verbal WM may be less sensitive to reward effects than systems recruited for spatial WM (Thomason et al., 2009), though further studies are needed to confirm this. Similarly, one study using a spatial WM task did demonstrate improvements in patients with SCZ in response to social rewards (Park, Gibson, & McMichael, 2006). While cognitive training ((Adcock et al., 2009; Kurtz & Richardson, 2012; Ramsay & MacDonald, 2015; Wexler, Anderson, Fulbright, & Gore, 2000), though see (Fisher et al., 2015)) is often studied, harnessing the reward system for cognitive improvement may also prove to be important. Carefully characterizing the neural substrates driving this effect will be an important next step.

Contextually Presented Rewards Do Not Improve WM Performance in Patients with SCZ.

This study additionally examined contextually presented rewards over a block of WM trials without cues or reminders, and demonstrated a lack of improvement in WM performance in SCZ. Our finding is in line with prior work suggesting that context maintenance, which is disrupted in SCZ, is critical for longer-term reward representation (Barch et al., 2003;

Braver, Barch, & Cohen, 1999; Cohen & Servan-Schreiber, 1992; Javitt, Shelley, Silipo, & Lieberman, 2000; MacDonald & Carter, 2003; Stratta, Daneluzzo, Bustini, Prosperini, & Rossi, 2000). In our work, patients with SCZ were unable to improve spatial WM performance in contextually rewarded WM trials, and had significant performance differences between context and trial rewarded conditions. Conversely, HCS demonstrated a larger effect size between performances in contextually rewarded and neutral conditions, and a more similar performance between context and trial rewarded conditions, though we also acknowledge the trend towards significance. Our exploratory follow-up analysis demonstrated some evidence that patients with SCZ understood the rewarding context, and that, over the course of the block, their performance declined, perhaps due to degradation of reward representations. Taken together, our results give some evidence that patients with SCZ can utilize cognitive resources to take advantage of moment-by-moment rewards, but we speculate that these resources are taxed when forced to keep in mind the context of reward, without cues or reminders. Interestingly, that patients with SCZ can take advantage of these rewards over shorter periods of time fits well with prior work demonstrating intact reward consumption, but disrupted reward anticipation and recall in SCZ (Berenbaum & Oltmanns, 1992; Blanchard et al., 1994; Dowd & Barch, 2010; Gard et al., 2007; Heerey & Gold, 2007; Kring & Neale, 1996; Ursu et al., 2011). Over time, such difficulty with reward representation may explain why patients with SCZ look less forward to, and engage less in, goal-directed activities requiring longer-term maintenance of potentially rewarding outcomes (Gard et al., 2007). Notably, the interaction of reward-cognition disruptions with time is not yet known, as the context condition within our task was presented over minutes, yet newer assessments such as the CAINS (Clinical Assessment Interview for Negative Symptoms) quantify amotivation and other negative symptoms over a week (Kring, Gur, Blanchard, Horan, & Reise, 2013).

Given previously noted contextual processing deficits reported in patients with SCZ,(Barch et al., 2003; Braver et al., 1999; Cohen & Servan-Schreiber, 1992; Javitt et al., 2000; Servan-Schreiber, Cohen, & Steingard, 1996; Stratta et al., 2000), it is unclear whether the inability of patients with SCZ to be influenced by contextual rewards is due to emotional content, rather than simply contextual presentation. Other work suggests that patients with SCZ do have difficulty maintaining emotional experiences, particularly when recalling such experiences (Gard et al., 2011; Holt et al., 2009), and exhibit inappropriately diminished startle responses after emotional stimuli disappear (Kring, Germans Gard, & Gard, 2011). Interestingly, in our study, baseline spatial WM performance was not associated with improvement in contextually rewarded trials, possibly because of modest improvement. The modest improvement in the contextual block was somewhat surprising in HCS, given previous work (Chiew & Braver, 2013; Jimura et al., 2010), however task differences, and possibly, lack of counterbalancing may account for this. Furthermore, our current design may not have been salient enough for engagement (e.g. more monetary reward may be needed). Future work may consider parametric manipulation of the magnitude of contextual reward to examine if this effect increases in relation to greater rewarding context. Finally it is worth highlighting that, overall, our behavioral findings are most relevant to young adults and adults in the early course of SCZ, given the age range of our subjects. Given the scant literature on reward-WM interactions in patients with SCZ, it is difficult to know whether

our results are specific to early-course illness or generalizable across the phases of illness. Probing for developmental differences and similarities in reward-cognition interactions across the lifespan of patients with SCZ represents an intriguing aim for future experiments.

Increased Inhibition or Strengthening of Cortical WM Circuits May Increase WM Precision.

Our biophysically-based computational model of WM in association cortical circuits generated the hypothesis that increased feed-forward GABAergic inhibition and recurrent scaling of local synapses my be possible microcircuit mechanisms that contribute to the improved WM performance noted in our behavioral study. Biologically, the two computational manipulations have the potential to capture a reward-related input, through afferent input or neurotransmitter modulation, respectively, and may correspond to the diverse cortical and subcortical inputs to the prefrontal cortex, and the rich catecholaminergic influence on spatial WM performance documented in primates (Arnsten et al., 1994; Arnsten, Wang, & Paspalas, 2015; Barbas & Pandya, 1989; Petrides & Pandya, 1999; Williams & Goldman-Rakic, 1998). However, these two mechanisms appeared to differentially influence neuronal firing, with local recurrent scaling increasing neuronal firing, and feed-forward inhibition decreasing neuronal firing. Additionally, feed-forward inhibition led to the eventual breakdown of WM precision, suggesting a more limited mechanism to improve WM precision. Thus, while both modulations improved WM precision, the underlying effects appeared different, warranting future studies of this model and explicit experimental testing. For instance, one hypothesis testable through clinical neuroimaging would be that the neuromodulatory impact onto the WM cortical circuit may originate subcortically, whereas the feed-forward GABAergic inhibition may be cortico-cortical in origin.

Each manipulation appeared to be possible mechanisms for both HCS and patients with SCZ, as demonstrated by the ‘control’ and ‘disinhibited’ models, respectively. The emergence of these mechanisms as possible processes for improved WM performance additionally highlights potential targets for improving WM performance in patients with SCZ. For instance, it is possible to speculate that in vivo experimentation using pharmacologic agents that target either increased feedforward GABAergic inhibition, or recurrent scaling of synaptic strengths may result in improved WM performance. Ideally, such agents would be carefully designed to target the specific mechanisms and neuronal targets described above, with subsequent experimentation to understand their behavioral effects. The added dimension of microcircuit mechanisms hypothesized by computational modeling may thus prove useful in understanding not only differential pathophysiology, but also future treatment targets (Huys et al., 2016; Wang & Krystal, 2014).

Limitations.

While the study design has face validity to the construct of motivation, direct links between our findings and either symptomatology or measures of motivation were not incorporated. Results are most applicable to young adults and earlier course patients given our subject demographics. Our study design left mechanistic questions about the effect of feedback, general attention, arousal or cognitive control open (Chiew & Braver, 2013). In particular, given the apparent time-sensitivity of reward-cognition interactions in SCZ, it is possible

feedback may also serve as a short-term reminder of reward for upcoming trials. Our consistent presentation of the context block at the end of the task also may have confounded additional effects, such as fatigue, and future versions of this task may involve counter-balancing the conditions. We are also unable to comment on whether switching the association of the colors between the neutral WM trials and the context reward block contributed to the effect of the context reward block Finally, though our computational modeling represents proof-of-principle in bridging spatial WM bias following reward with neural circuit mechanisms, more advanced simulations and experiments are needed to mechanistically link levels of analyses. Furthermore, the quantitative fitting of individual-level behavior with biophysically-based circuit models remains an important challenge for this class of models. Advances in this direction will likely require applications of techniques such as mean-field analysis of neural dynamics and Bayesian model fitting (Ueltzhoffer, Armbruster-Genc, & Fiebach, 2015)

Conclusions.

This work examined the interface of reward processing and WM in patients with SCZ through the use of a rewarded spatial WM task. Patients with SCZ demonstrated improved spatial WM performance when rewards were provided on a short-term, trial-by-trial, basis. This improvement appeared dependent on baseline spatial WM capacity and general motor control. However, patients with SCZ showed no spatial WM improvement when rewards were provided contextually across a block of WM trials, implicating disrupted reward representations when forced to keep in mind a rewarding context. Computational modeling suggested that increased scaling of recurrent synaptic strengths and feed-forward inhibition in fronto-parietal circuits may be putative neuronal mechanisms underlying the ability to improve spatial WM precision. Collectively, this work demonstrates both preserved and disrupted features of reward-cognition interactions in patients with SCZ, suggesting the importance of cognitive reserve in motivational processes, and highlighting the need for carefully parsing the impact of reward on cognition in SCZ.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENTS:

This work was supported by the NARSAD Independent Investigator Award, NARSAD Young Investigator Award, 1DP5-OD012109, & R01 MH108590 (PI: Anticevic, A.). This work was supported by T32 MH019961 (YTC; PI: Robert T. Malison) and T32 MH018268 (YTC; PI: Michael J. Crowley).

REFERENCES

Adcock RA, Dale C, Fisher M, Aldebot S, Genevsky A, Simpson GV, . . . Vinogradov S (2009). When top-down meets bottom-up: auditory training enhances verbal memory in schizophrenia. Schizophrenia bulletin, 35(6), 1132–1141. doi:10.1093/schbul/sbp068 [PubMed: 19745022]

Andreasen N, & Grove W (1986). Evaluation of positive and negative symptoms in schizophrenia. Psychiatry and Psychobiology, 1, 108–121.

Andreasen NC, Pressler M, Nopoulos P, Miller D, & Ho BC (2010). Antipsychotic dose equivalents and dose-years: a standardized method for comparing exposure to different drugs. Biol Psychiatry, 67(3), 255–262. doi:10.1016/j.biopsych.2009.08.040 [PubMed: 19897178]

Anticevic A, Gancsos M, Murray JD, Repovs G, Driesen NR, Ennis DJ, . . . Corlett PR (2012). NMDA receptor function in large-scale anticorrelated neural systems with implications for cognition and schizophrenia. Proc Natl Acad Sci U S A, 109(41), 16720–16725. doi:10.1073/pnas.1208494109 [PubMed: 23012427]

Anticevic A, & Murray JD (2017). Computational Psychiatry, Mathematical Modeling of Mental Illness, 1st edition. Academic Press.

Arnsten AF (2011). Catecholamine influences on dorsolateral prefrontal cortical networks. Biological psychiatry, 69(12), e89–99. doi:10.1016/j.biopsych.2011.01.027 [PubMed: 21489408]

Arnsten AF, Cai JX, Murphy BL, & Goldman-Rakic PS (1994). Dopamine D1 receptor mechanisms in the cognitive performance of young adult and aged monkeys. Psychopharmacology, 116(2), 143–151. [PubMed: 7862943]

Arnsten AF, & Goldman-Rakic PS (1998). Noise stress impairs prefrontal cortical cognitive function in monkeys: evidence for a hyperdopaminergic mechanism. Archives of general psychiatry, 55(4), 362–368. [PubMed: 9554432]

Arnsten AF, Wang M, & Paspalas CD (2015). Dopamine's Actions in Primate Prefrontal Cortex: Challenges for Treating Cognitive Disorders. Pharmacol Rev, 67(3), 681–696. doi:10.1124/pr.115.010512 [PubMed: 26106146]

Awh E, Jonides J, & Reuter-Lorenz PA (1998). Rehearsal in spatial working memory. Journal of experimental psychology. Human perception and performance, 24(3), 780–790. [PubMed: 9627416]

Barbas H, & Pandya DN (1989). Architecture and intrinsic connections of the prefrontal cortex in the rhesus monkey. The Journal of comparative neurology, 286(3), 353–375. doi:10.1002/cne.902860306 [PubMed: 2768563]

Barch DM, Carter CS, Braver TS, Sabb FW, MacDonald A, 3rd, Noll DC, & Cohen JD (2001). Selective deficits in prefrontal cortex function in medication-naive patients with schizophrenia. Archives of general psychiatry, 58(3), 280–288. [PubMed: 11231835]

Barch DM, Carter CS, MacDonald AW, 3rd, Braver TS, & Cohen JD (2003). Context-processing deficits in schizophrenia: diagnostic specificity, 4-week course, and relationships to clinical symptoms. Journal of abnormal psychology, 112(1), 132–143. [PubMed: 12653421]

Barch DM, & Dowd EC (2010). Goal representations and motivational drive in schizophrenia: the role of prefrontal-striatal interactions. Schizophrenia bulletin, 36(5), 919–934. doi:10.1093/schbul/sbq068 [PubMed: 20566491]

Beck SM, Locke HS, Savine AC, Jimura K, & Braver TS (2010). Primary and secondary rewards differentially modulate neural activity dynamics during working memory. PLoS One, 5(2), e9251. doi:10.1371/journal.pone.0009251 [PubMed: 20169080]

Belforte JE, Zsiros V, Sklar ER, Jiang Z, Yu G, Li Y, . . . Nakazawa K (2010). Postnatal NMDA receptor ablation in corticolimbic interneurons confers schizophrenia-like phenotypes. Nature neuroscience, 13(1), 76–83. doi:10.1038/nn.2447 [PubMed: 19915563]

Berenbaum H, & Oltmanns TF (1992). Emotional experience and expression in schizophrenia and depression. Journal of abnormal psychology, 101(1), 37–44. [PubMed: 1537971]

Berridge KC (2012). From prediction error to incentive salience: mesolimbic computation of reward motivation. The European journal of neuroscience, 35(7), 1124–1143. doi:10.1111/j.1460-9568.2012.07990.x [PubMed: 22487042]

Blanchard JJ, Bellack AS, & Mueser KT (1994). Affective and social-behavioral correlates of physical and social anhedonia in schizophrenia. Journal of abnormal psychology, 103(4), 719–728. [PubMed: 7822573]

Braver TS, Barch DM, & Cohen JD (1999). Cognition and control in schizophrenia: a computational model of dopamine and prefrontal function. Biological psychiatry, 46(3), 312–328. [PubMed: 10435197]

Brunel N, & Wang X (2001). Effects of neuromodulation in a cortical network model of object working memory dominated by recurrent inhibition. Journal of computational neuroscience, 11(1), 63–85. [PubMed: 11524578]

Burbridge JA, & Barch DM (2007). Anhedonia and the experience of emotion in individuals with schizophrenia. Journal of abnormal psychology, 116(1), 30–42. doi:10.1037/0021-843X.116.1.30 [PubMed: 17324014]

Carter E, & Wang XJ (2007). Cannabinoid-mediated disinhibition and working memory: dynamical interplay of multiple feedback mechanisms in a continuous attractor model of prefrontal cortex. Cerebral cortex, 17 Suppl 1, i16–26. doi:10.1093/cercor/bhm103 [PubMed: 17725998]

Chiew KS, & Braver TS (2013). Temporal dynamics of motivation-cognitive control interactions revealed by high-resolution pupillometry. Frontiers in psychology, 4, 15. doi:10.3389/fpsyg.2013.00015 [PubMed: 23372557]

Chiew KS, & Braver TS (2014). Dissociable influences of reward motivation and positive emotion on cognitive control. Cogn Affect Behav Neurosci, 14(2), 509–529. doi:10.3758/s13415-014-0280-0 [PubMed: 24733296]

Cohen JD, & Servan-Schreiber D (1992). Context, cortex, and dopamine: a connectionist approach to behavior and biology in schizophrenia. Psychol Rev, 99(1), 45–77. [PubMed: 1546118]

Compte A, Brunel N, Goldman-Rakic PS, & Wang XJ (2000). Synaptic mechanisms and network dynamics underlying spatial working memory in a cortical network model. Cerebral cortex, 10(9), 910–923. [PubMed: 10982751]

Deco G, & Rolls ET (2003). Attention and working memory: a dynamical model of neuronal activity in the prefrontal cortex. The European journal of neuroscience, 18(8), 2374–2390. [PubMed: 14622200]

Dixon ML, & Christoff K (2012). The decision to engage cognitive control is driven by expected reward-value: neural and behavioral evidence. PloS one, 7(12), e51637. doi:10.1371/journal.pone.0051637 [PubMed: 23284730]

Dowd EC, & Barch DM (2010). Anhedonia and emotional experience in schizophrenia: neural and behavioral indicators. Biol Psychiatry, 67(10), 902–911. doi:10.1016/j.biopsych.2009.10.020 [PubMed: 20004364]

Driesen NR, McCarthy G, Bhagwagar Z, Bloch MH, Calhoun VD, D'Souza DC, . . . Krystal JH (2013). The impact of NMDA receptor blockade on human working memory-related prefrontal function and connectivity. Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology, 38(13), 2613–2622. doi:10.1038/npp.2013.170 [PubMed: 23856634]

Fioravanti M, Bianchi V, & Cinti ME (2012). Cognitive deficits in schizophrenia: an updated metanalysis of the scientific evidence. BMC Psychiatry, 12, 64. doi:10.1186/1471-244X-12-64 [PubMed: 22715980]

First MB, Spitzer RL, Gibbon M, & Williams JBW (2002). Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Research Version, Patient Edition. (SCID-I/P) New York: Biometrics Research, New York State Psychiatric Institute.

Fisher M, Loewy R, Carter C, Lee A, Ragland JD, Niendam T, . . . Vinogradov S (2015). Neuroplasticity-based auditory training via laptop computer improves cognition in young individuals with recent onset schizophrenia. Schizophrenia bulletin, 41(1), 250–258. doi:10.1093/schbul/sbt232 [PubMed: 24444862]

Forbes NF, Carrick LA, McIntosh AM, & Lawrie SM (2009). Working memory in schizophrenia: a meta-analysis. Psychological medicine, 39(6), 889–905. doi:10.1017/S0033291708004558 [PubMed: 18945379]

Foussias G, Mann S, Zakzanis KK, van Reekum R, Agid O, & Remington G (2011). Prediction of longitudinal functional outcomes in schizophrenia: the impact of baseline motivational deficits. Schizophrenia research, 132(1), 24–27. doi:10.1016/j.schres.2011.06.026 [PubMed: 21771567]

Funahashi S, Bruce CJ, & Goldman-Rakic PS (1989). Mnemonic coding of visual space in the monkey's dorsolateral prefrontal cortex. Journal of neurophysiology, 61(2), 331–349. [PubMed: 2918358]

Gard DE, Cooper S, Fisher M, Genevsky A, Mikels JA, & Vinogradov S (2011). Evidence for an emotion maintenance deficit in schizophrenia. Psychiatry research, 187(1–2), 24–29. doi:10.1016/j.psychres.2010.12.018 [PubMed: 21237516]

Gard DE, Kring AM, Gard MG, Horan WP, & Green MF (2007). Anhedonia in schizophrenia: distinctions between anticipatory and consummatory pleasure. Schizophrenia research, 93(1–3), 253–260. doi:10.1016/j.schres.2007.03.008 [PubMed: 17490858]

Godijn R, & Theeuwes J (2012). Overt is no better than covert when rehearsing visuo-spatial information in working memory. Mem Cognit, 40(1), 52–61. doi:10.3758/s13421-011-0132-x

Gold JM, Waltz JA, Prentice KJ, Morris SE, & Heerey EA (2008). Reward processing in schizophrenia: a deficit in the representation of value. Schizophrenia bulletin, 34(5), 835–847. doi:10.1093/schbul/sbn068 [PubMed: 18591195]

Goldman-Rakic PS (1999). The physiological approach: functional architecture of working memory and disordered cognition in schizophrenia. Biological psychiatry, 46(5), 650–661. [PubMed: 10472417]

Green MF (1996). What are the functional consequences of neurocognitive deficits in schizophrenia? The American journal of psychiatry, 153(3), 321–330. doi:10.1176/ajp.153.3.321 [PubMed: 8610818]

Hager OM, Kirschner M, Bischof M, Hartmann-Riemer MN, Kluge A, Seifritz E, . . . Kaiser S (2015). Reward-dependent modulation of working memory is associated with negative symptoms in schizophrenia. Schizophrenia research, 168(1–2), 238–244. doi:10.1016/j.schres.2015.08.024 [PubMed: 26362736]

Harvey PD, Koren D, Reichenberg A, & Bowie CR (2006). Negative symptoms and cognitive deficits: what is the nature of their relationship? Schizophrenia bulletin, 32(2), 250–258. doi:10.1093/schbul/sbj011 [PubMed: 16221995]

Heerey EA, Bell-Warren KR, & Gold JM (2008). Decision-making impairments in the context of intact reward sensitivity in schizophrenia. Biological psychiatry, 64(1), 62–69. doi:10.1016/j.biopsych.2008.02.015 [PubMed: 18377874]

Heerey EA, & Gold JM (2007). Patients with schizophrenia demonstrate dissociation between affective experience and motivated behavior. Journal of abnormal psychology, 116(2), 268–278. doi:10.1037/0021-843X.116.2.268 [PubMed: 17516760]

Heerey EA, Matveeva TM, & Gold JM (2011). Imagining the future: degraded representations of future rewards and events in schizophrenia. Journal of abnormal psychology, 120(2), 483–489. doi:10.1037/a0021810 [PubMed: 21171727]

Heinrichs RW, & Zakzanis KK (1998). Neurocognitive deficit in schizophrenia: a quantitative review of the evidence. Neuropsychology, 12(3), 426–445. [PubMed: 9673998]

Holt DJ, Lebron-Milad K, Milad MR, Rauch SL, Pitman RK, Orr SP, . . . Goff DC (2009). Extinction memory is impaired in schizophrenia. Biological psychiatry, 65(6), 455–463. doi:10.1016/j.biopsych.2008.09.017 [PubMed: 18986648]

Huys QJ, Maia TV, & Frank MJ (2016). Computational psychiatry as a bridge from neuroscience to clinical applications. Nature neuroscience, 19(3), 404–413. doi:10.1038/nn.4238 [PubMed: 26906507]

Javitt DC, Shelley AM, Silipo G, & Lieberman JA (2000). Deficits in auditory and visual context-dependent processing in schizophrenia: defining the pattern. Archives of general psychiatry, 57(12), 1131–1137. [PubMed: 11115326]

Jimura K, Locke HS, & Braver TS (2010). Prefrontal cortex mediation of cognitive enhancement in rewarding motivational contexts. Proceedings of the National Academy of Sciences of the United States of America, 107(19), 8871–8876. doi:10.1073/pnas.1002007107 [PubMed: 20421489]

Juckel G, Schlagenhauf F, Koslowski M, Wustenberg T, Villringer A, Knutson B, . . . Heinz A (2006). Dysfunction of ventral striatal reward prediction in schizophrenia. Neuroimage, 29(2), 409–416. [PubMed: 16139525]

Kay SR, Fiszbein A, & Opler LA (1987). The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophrenia bulletin, 13(2), 261–276. [PubMed: 3616518]

Kennerley SW, & Wallis JD (2009). Reward-dependent modulation of working memory in lateral prefrontal cortex. The Journal of neuroscience : the official journal of the Society for Neuroscience, 29(10), 3259–3270. doi:10.1523/JNEUROSCI.5353-08.2009 [PubMed: 19279263]

Krawczyk DC, Gazzaley A, & D'Esposito M (2007). Reward modulation of prefrontal and visual association cortex during an incentive working memory task. Brain research, 1141, 168–177. doi:10.1016/j.brainres.2007.01.052 [PubMed: 17320835]

Kring AM, Germans Gard M, & Gard DE (2011). Emotion deficits in schizophrenia: timing matters. Journal of abnormal psychology, 120(1), 79–87. doi:10.1037/a0021402 [PubMed: 21058754]

Kring AM, Gur RE, Blanchard JJ, Horan WP, & Reise SP (2013). The Clinical Assessment Interview for Negative Symptoms (CAINS): final development and validation. The American journal of psychiatry, 170(2), 165–172. doi:10.1176/appi.ajp.2012.12010109 [PubMed: 23377637]

Kring AM, & Neale JM (1996). Do schizophrenic patients show a disjunctive relationship among expressive, experiential, and psychophysiological components of emotion? Journal of abnormal psychology, 105(2), 249–257. [PubMed: 8723006]

Krystal JH, D'Souza DC, Mathalon D, Perry E, Belger A, & Hoffman R (2003). NMDA receptor antagonist effects, cortical glutamatergic function, and schizophrenia: toward a paradigm shift in medication development. Psychopharmacology, 169(3–4), 215–233. doi:10.1007/s00213-003-1582-z [PubMed: 12955285]

Kumari SM,M; Florival C; Manalai P; Sonje S;. (2017). An Assessment of Five (PANSS, SAPS, SANS, NSA-16, CGI-SCH) commonly used Symptoms Rating Scales in Schizophrenia and Comparision to Newer Scales (CAINS, BNSS). Journal of Addiction Research and Therapy, 8(3), 1–7.

Kurtz MM, & Richardson CL (2012). Social cognitive training for schizophrenia: a meta-analytic investigation of controlled research. Schizophrenia bulletin, 38(5), 1092–1104. doi:10.1093/schbul/sbr036 [PubMed: 21525166]

Lawrence BM, Myerson J, & Abrams RA (2004). Interference with spatial working memory: an eye movement is more than a shift of attention. Psychonomic bulletin & review, 11(3), 488–494. [PubMed: 15376800]

Lee J, & Park S (2005). Working memory impairments in schizophrenia: a meta-analysis. Journal of abnormal psychology, 114(4), 599–611. doi:10.1037/0021-843X.114.4.599 [PubMed: 16351383]

Lewis DA, & Lieberman JA (2000). Catching up on schizophrenia: natural history and neurobiology. Neuron, 28(2), 325–334. [PubMed: 11144342]

Locke HS, & Braver TS (2008). Motivational influences on cognitive control: behavior, brain activation, and individual differences. Cogn Affect Behav Neurosci, 8(1), 99–112. [PubMed: 18405050]

MacDonald AW, 3rd, & Carter CS (2003). Event-related FMRI study of context processing in dorsolateral prefrontal cortex of patients with schizophrenia. Journal of abnormal psychology, 112(4), 689–697. doi:10.1037/0021-843X.112.4.689 [PubMed: 14674880]

Marder SR, & Galderisi S (2017). The current conceptualization of negative symptoms in schizophrenia. World psychiatry : official journal of the World Psychiatric Association, 16(1), 14–24. doi:10.1002/wps.20385

Milev P, Ho BC, Arndt S, & Andreasen NC (2005). Predictive values of neurocognition and negative symptoms on functional outcome in schizophrenia: a longitudinal first-episode study with 7-year follow-up. The American journal of psychiatry, 162(3), 495–506. doi:10.1176/appi.ajp.162.3.495 [PubMed: 15741466]

Murray JD, Anticevic A, Gancsos M, Ichinose M, Corlett PR, Krystal JH, & Wang XJ (2014). Linking microcircuit dysfunction to cognitive impairment: effects of disinhibition associated with schizophrenia in a cortical working memory model. Cerebral cortex, 24(4), 859–872. doi:10.1093/cercor/bhs370 [PubMed: 23203979]

Nielsen MO, Rostrup E, Wulff S, Bak N, Broberg BV, Lublin H, . . . Glenthoj B (2012). Improvement of brain reward abnormalities by antipsychotic monotherapy in schizophrenia. Archives of general psychiatry, 69(12), 1195–1204. doi:10.1001/archgenpsychiatry.2012.847 [PubMed: 22868877]

Nielsen MO, Rostrup E, Wulff S, Bak N, Lublin H, Kapur S, & Glenthoj B (2012). Alterations of the brain reward system in antipsychotic naive schizophrenia patients. Biological psychiatry, 71(10), 898–905. doi:10.1016/j.biopsych.2012.02.007 [PubMed: 22418013]

Park S, Gibson C, & McMichael T (2006). Socioaffective factors modulate working memory in schizophrenia patients. Neuroscience, 139(1), 373–384. doi:10.1016/j.neuroscience.2005.06.034 [PubMed: 16337745]

Pearson DG, Ball K, & Smith DT (2014). Oculomotor preparation as a rehearsal mechanism in spatial working memory. Cognition, 132(3), 416–428. doi:10.1016/j.cognition.2014.05.006 [PubMed: 24908341]

Petrides M, & Pandya DN (1999). Dorsolateral prefrontal cortex: comparative cytoarchitectonic analysis in the human and the macaque brain and corticocortical connection patterns. The European journal of neuroscience, 11(3), 1011–1036. [PubMed: 10103094]

Pochon JB, Levy R, Fossati P, Lehericy S, Poline JB, Pillon B, . . . Dubois B (2002). The neural system that bridges reward and cognition in humans: an fMRI study. Proceedings of the National Academy of Sciences of the United States of America, 99(8), 5669–5674. doi:10.1073/pnas.082111099 [PubMed: 11960021]

Postle BR, Idzikowski C, Sala SD, Logie RH, & Baddeley AD (2006). The selective disruption of spatial working memory by eye movements. Quarterly journal of experimental psychology, 59(1), 100–120. doi:10.1080/17470210500151410

Radua J, Schmidt A, Borgwardt S, Heinz A, Schlagenhauf F, McGuire P, & Fusar-Poli P (2015). Ventral Striatal Activation During Reward Processing in Psychosis: A Neurofunctional Meta-Analysis. JAMA Psychiatry, 72(12), 1243–1251. doi:10.1001/jamapsychiatry.2015.2196 [PubMed: 26558708]

Ramsay IS, & MacDonald AW, 3rd. (2015). Brain Correlates of Cognitive Remediation in Schizophrenia: Activation Likelihood Analysis Shows Preliminary Evidence of Neural Target Engagement. Schizophrenia bulletin, 41(6), 1276–1284. doi:10.1093/schbul/sbv025 [PubMed: 25800249]

Reddy LF, Horan WP, & Green MF (2016). Motivational Deficits and Negative Symptoms in Schizophrenia: Concepts and Assessments. Current topics in behavioral neurosciences, 27, 357–373. doi:10.1007/7854_2015_379 [PubMed: 26164592]

Richardson DC, & Spivey MJ (2000). Representation, space and Hollywood Squares: looking at things that aren't there anymore. Cognition, 76(3), 269–295. [PubMed: 10913578]

Rowe JB, Eckstein D, Braver T, & Owen AM (2008). How does reward expectation influence cognition in the human brain? Journal of cognitive neuroscience, 20(11), 1980–1992. doi:10.1162/jocn.2008.20140 [PubMed: 18416677]

Schlosser DA, Fisher M, Gard D, Fulford D, Loewy RL, & Vinogradov S (2014). Motivational deficits in individuals at-risk for psychosis and across the course of schizophrenia. Schizophrenia research, 158(1–3), 52–57. doi:10.1016/j.schres.2014.06.024 [PubMed: 25008792]

Servan-Schreiber D, Cohen JD, & Steingard S (1996). Schizophrenic deficits in the processing of context. A test of a theoretical model. Archives of general psychiatry, 53(12), 1105–1112. [PubMed: 8956676]

Spivey MJ, & Geng JJ (2001). Oculomotor mechanisms activated by imagery and memory: eye movements to absent objects. Psychological research, 65(4), 235–241. [PubMed: 11789427]

Stratta P, Daneluzzo E, Bustini M, Prosperini P, & Rossi A (2000). Processing of context information in schizophrenia: relation to clinical symptoms and WCST performance. Schizophrenia research, 44(1), 57–67. [PubMed: 10867312]

Summerfelt AT, Alphs LD, Wagman AM, Funderburk FR, Hierholzer RM, & Strauss ME (1991). Reduction of perseverative errors in patients with schizophrenia using monetary feedback. Journal of abnormal psychology, 100(4), 613–616. [PubMed: 1757677]

Taylor SF, Welsh RC, Wager TD, Phan KL, Fitzgerald KD, & Gehring WJ (2004). A functional neuroimaging study of motivation and executive function. NeuroImage, 21(3), 1045–1054. doi:10.1016/j.neuroimage.2003.10.032 [PubMed: 15006672]

Thomason ME, Race E, Burrows B, Whitfield-Gabrieli S, Glover GH, & Gabrieli JD (2009). Development of spatial and verbal working memory capacity in the human brain. Journal of cognitive neuroscience, 21(2), 316–332. doi:10.1162/jocn.2008.21028 [PubMed: 18510448]

Thornton AE, Boudreau VG, Griffiths SY, Woodward TS, Fawkes-Kirby T, & Honer WG (2007). The impact of monetary reward on memory in schizophrenia spectrum disorder. Neuropsychology, 21(5), 631–645. doi:10.1037/0894-4105.21.5.631 [PubMed: 17784811]

Tremblay S, Saint-Aubin J, & Jalbert A (2006). Rehearsal in serial memory for visual-spatial information: evidence from eye movements. Psychonomic bulletin & review, 13(3), 452–457. [PubMed: 17048730]

Ueltzhoffer K, Armbruster-Genc DJ, & Fiebach CJ (2015). Stochastic Dynamics Underlying Cognitive Stability and Flexibility. PLoS computational biology, 11(6), e1004331. doi:10.1371/journal.pcbi.1004331 [PubMed: 26068119]

Ursu S, Kring AM, Gard MG, Minzenberg MJ, Yoon JH, Ragland JD, . . . Carter CS (2011). Prefrontal cortical deficits and impaired cognition-emotion interactions in schizophrenia. The American journal of psychiatry, 168(3), 276–285. doi:10.1176/appi.ajp.2010.09081215 [PubMed: 21205806]

van Erp TG, Preda A, Nguyen D, Faziola L, Turner J, Bustillo J, . . . Fbirn. (2014). Converting positive and negative symptom scores between PANSS and SAPS/SANS. Schizophrenia research, 152(1), 289–294. doi:10.1016/j.schres.2013.11.013 [PubMed: 24332632]

Van Snellenberg JX, Torres IJ, & Thornton AE (2006). Functional neuroimaging of working memory in schizophrenia: task performance as a moderating variable. Neuropsychology, 20(5), 497–510. doi:10.1037/0894-4105.20.5.497 [PubMed: 16938013]

Vijayraghavan S, Wang M, Birnbaum SG, Williams GV, & Arnsten AF (2007). Inverted-U dopamine D1 receptor actions on prefrontal neurons engaged in working memory. Nature neuroscience, 10(3), 376–384. doi:10.1038/nn1846 [PubMed: 17277774]

Wang XJ, & Krystal JH (2014). Computational psychiatry. Neuron, 84(3), 638–654. doi:10.1016/j.neuron.2014.10.018 [PubMed: 25442941]

Watanabe M, Hikosaka K, Sakagami M, & Shirakawa S (2002). Coding and monitoring of motivational context in the primate prefrontal cortex. The Journal of neuroscience : the official journal of the Society for Neuroscience, 22(6), 2391–2400. [PubMed: 11896178]

Wexler BE, Anderson M, Fulbright RK, & Gore JC (2000). Preliminary evidence of improved verbal working memory performance and normalization of task-related frontal lobe activation in schizophrenia following cognitive exercises. The American journal of psychiatry, 157(10), 1694–1697. doi:10.1176/appi.ajp.157.10.1694 [PubMed: 11007730]

Williams SM, & Goldman-Rakic PS (1998). Widespread origin of the primate mesofrontal dopamine system. Cerebral cortex, 8(4), 321–345. [PubMed: 9651129]

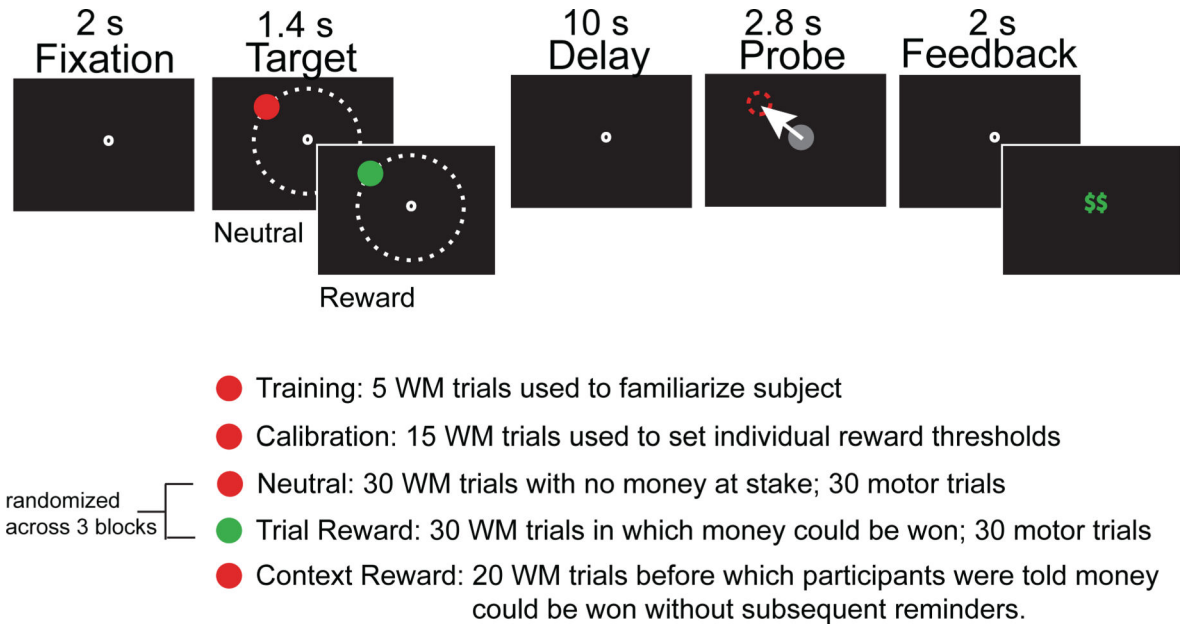

Figure 1. Spatial WM-Reward Task Design.

Each trial required subjects to remember the location of a circle after it disappeared. The task began with a period of central fixation (Fixation), followed by target presentation in one of 20 pseudo-randomized positions arranged in a 415-pixel radius ring from the center (Target). Target position was randomized throughout the task, and unknown to subjects. Once the target disappeared, the subject maintained the memory of the initial target location while continuing central fixation (Delay). A gray circle with positioning attached to a joystick (Probe) appeared and subjects moved the gray circle to where they remembered the target to be. The target was green in the Trial Reward types, and red elsewhere, with descriptions above. Rewarded trials were designed similarly, except for a green colored target to indicate the possibility for reward, and a feedback phase to indicate how well the subject performed. For the block of contextually rewarded trials, the cue was colored red, and subjects were instructed at the start of the block that there was the possibility to win money on each trial and they would not be reminded of this once the block started.

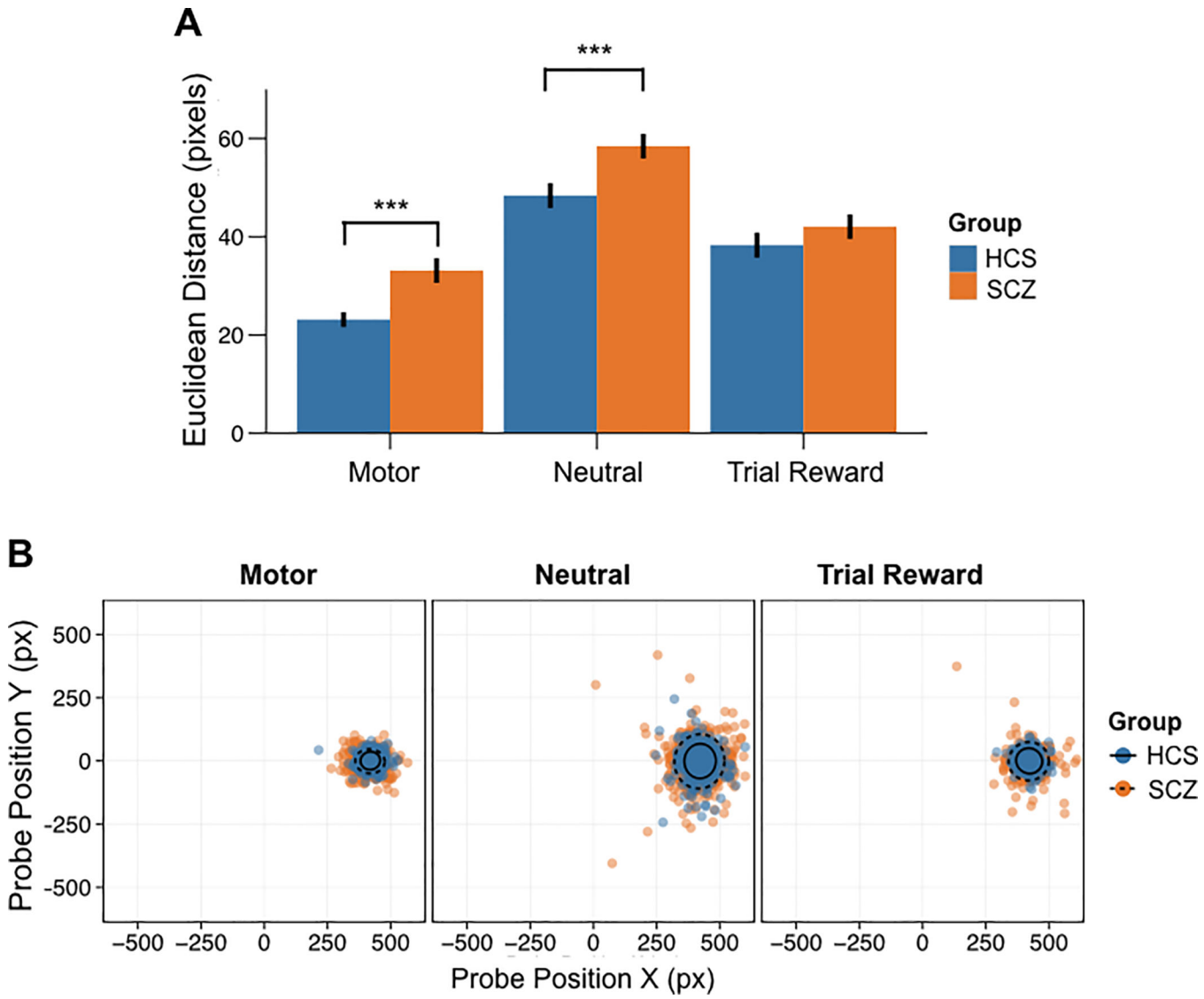

Figure 2. Effect of Reward on WM Performance.

A. Overall, patients with SCZ demonstrated significantly worse baseline motor and WM performance (as measured by Euclidean distance between target presentation and probe placement), compared to HCS (*** denotes $p<0.001$). There was a significant *WM x Group* interaction, $p<0.005$. Both groups demonstrated relative improvement in WM performance under trial reward conditions (adjusted means shown). Error bars represent SEM (adjusted). B. Scatterplot of raw responses following rotation of all target presentations to (415, 0) under motor, WM (neutral) and trial reward conditions. Compared to HCS, patients with SCZ demonstrated less accuracy across all three conditions. Ellipses show 95% confidence intervals.

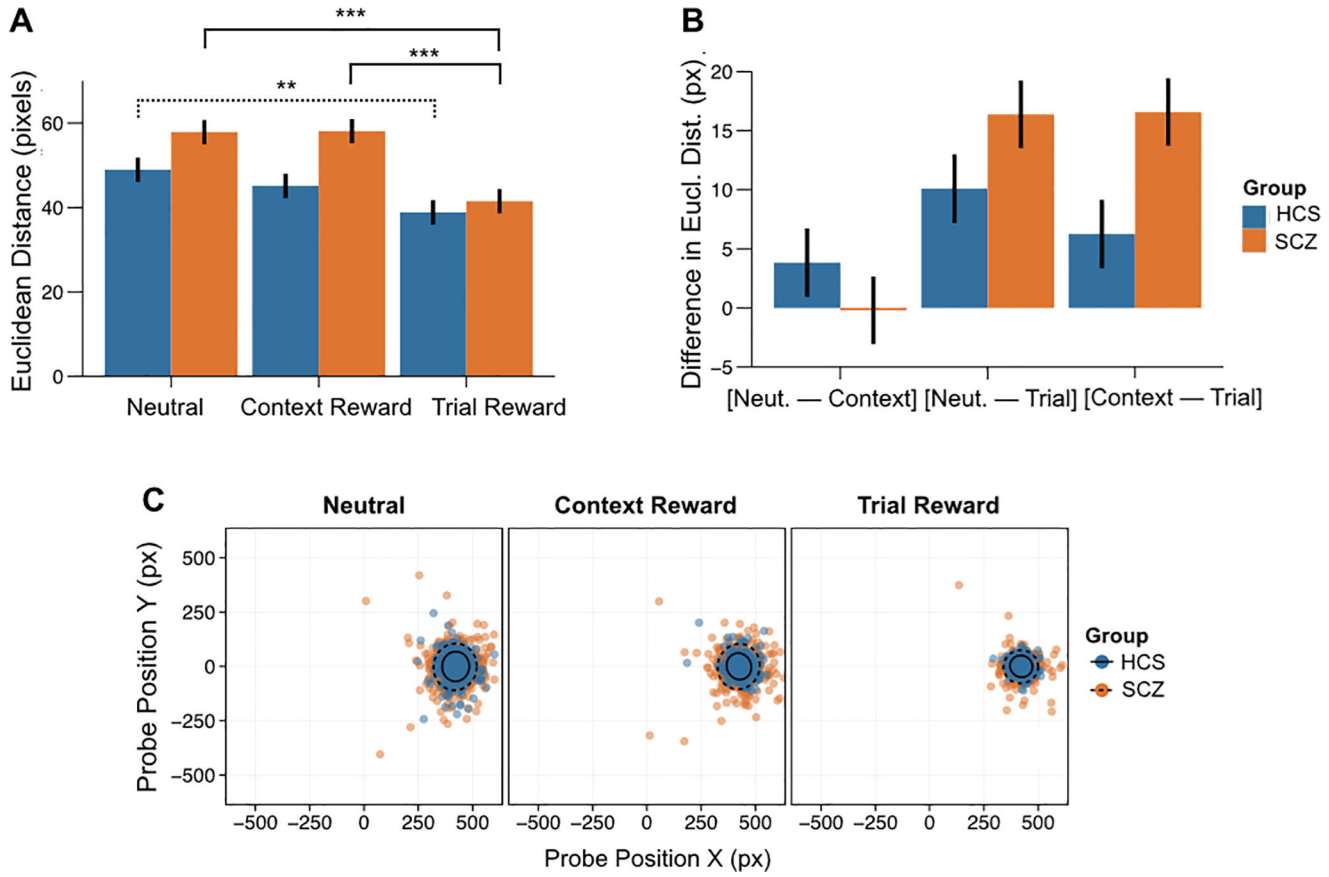

Figure 3. Effects of Contextually Presented Rewards on WM Performance.

A. Adjusted mean spatial WM performance under neutral, contextually rewarded, and trial rewarded conditions for each group. There was a significant interaction of *Context* x *Group* ($p<0.05$). Examination of this interaction demonstrated differential performance between contextually presented and trial rewards in patients with SCZ ($p<0.001$, $d=-1.01$), with less differentiation for HCS ($p>0.05$, $d=-0.38$). Patients with SCZ demonstrated no performance improvement in response to contextually presented rewards ($p>0.1$, $d=0.01$), while HCS showed modest improvement ($p>0.05$, $d = -0.23$). Each group demonstrated improved WM performance when rewards were presented in a trial-by-trial manner compared to neutral trials (*** denotes $p<0.001$; ** denotes $p<0.005$). Error bars are adjusted SEM. B. Plot demonstrating the adjusted change in WM performance between groups. [Neut. — Context] refers to the change in WM performance between the neutral condition and the context reward condition; [Neut. — Trial] refers to the change in WM performance between the neutral condition and the trial reward condition; [Context – Trial] refers to the change in WM performance between the context reward and trial reward condition. Error bars are adjusted SEM. C. Scatter plot showing raw distribution of responses following rotation of all target presentations to (415, 0). Ellipses represent 95% CI.

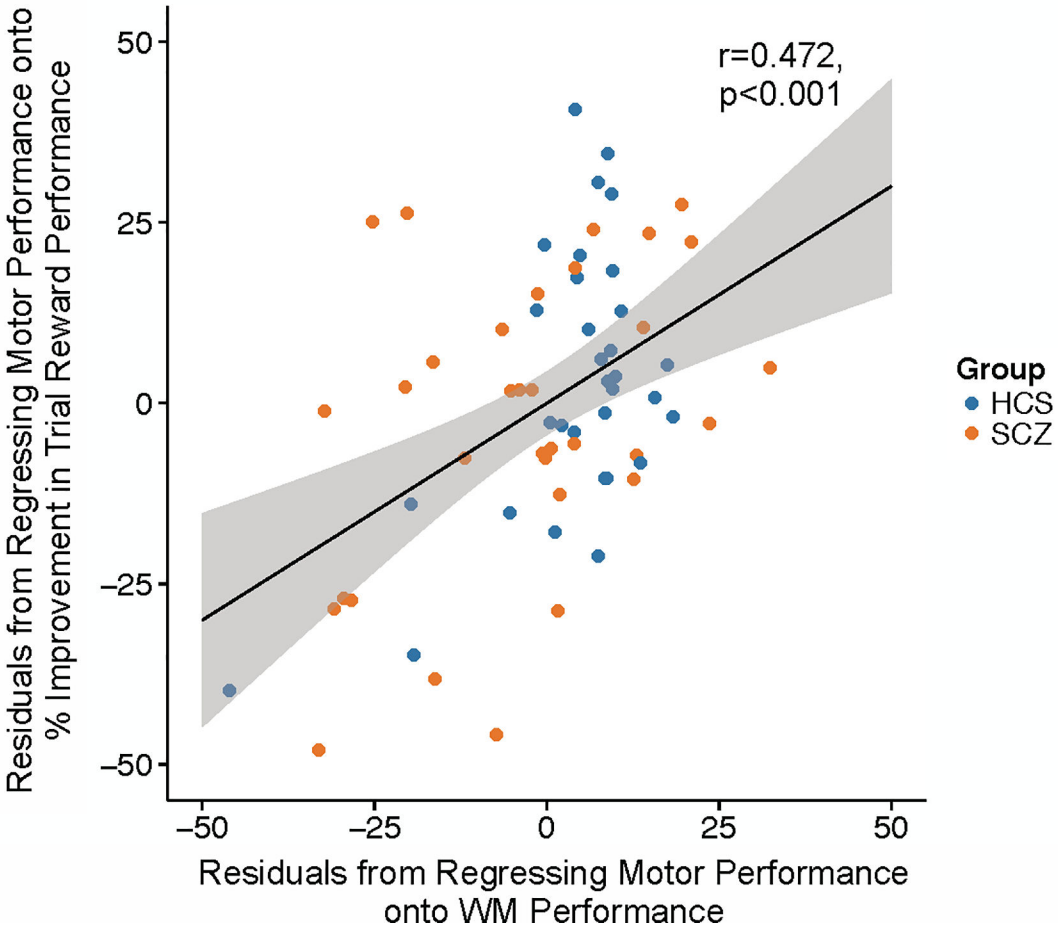

Figure 4. Partial Correlation of WM Performance and Percent Improvement in Trial Reward When Controlling for Motor Performance.

Worse baseline WM performance in neutral trials was significantly correlated with greater percent improvement in trial reward performance when controlling for motor performance ($r = 0.472$, $p<0.001$). This suggests that baseline cognitive performance did not preclude improvement in response to short-term rewards. Shaded areas indicate 95% CI.

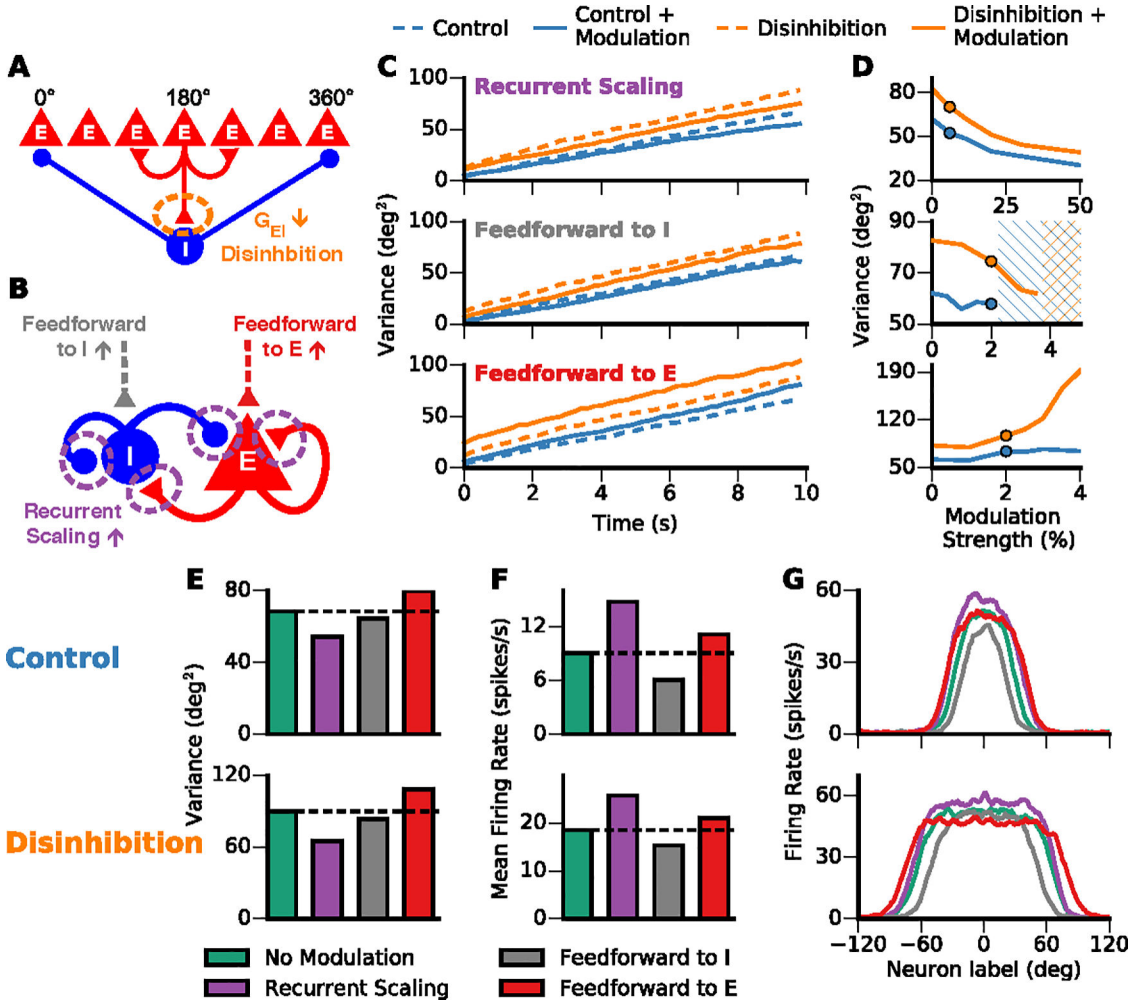

Figure 5. Modulation of WM Precision in a Fronto-Parietal Cortical Circuit Model.

(A) The model architecture consisted of recurrently connected excitatory pyramidal cells (E) and inhibitory interneurons (I). Pyramidal cells are labeled by the angular location they were tuned to (0–360°). E-to-E connections were structured and stronger for neurons with similar preferred angles, while all recurrent connections involving I-cells were unstructured and mediated feedback inhibition. Cortical disinhibition was implemented through NMDAR hypo-function on interneurons (decreased NMDA receptor conductance on interneurons, G_{EI}, by 3.25%), weakening recruitment of feedback inhibition. **(B)** Three candidate mechanisms for modulation of the WM circuit by reward-related signals: (i) neuromodulatory positive scaling of recurrent NMDA and GABA receptor conductances (default value of 6%) (purple), (ii) increased feedforward glutamatergic background drive to I-cells (default value of 2%) (gray), and (iii) increased background drive to E-cells (default value of 2%) (red). **(C)** Variance of the encoded angle grew with time during the delay period, indicating decreased WM precision. Disinhibition (orange) decreased precision (i.e., higher variance) compared to the control condition (blue). The three modulations altered WM precision (dashed for no modulation, solid for modulation): precision improved (lower variance, in line with empirical reward effects) with either recurrent scaling (top) or feedforward drive to I-cells (middle), whereas precision worsened (higher variance) with

feedforward drive to E-cells (bottom). **(D)** WM precision changed parametrically over a range of modulation strengths. The variance plotted was from the end of the 10-s delay. Note that recurrent scaling was the only manipulation that was stable under strong modulations. For an increase of feedforward drive to I-cells beyond a few percent, dominance of inhibition prevented WM-related persistent activity, for both control and disinhibition networks. The hashed areas of either color denote corresponding regions in which the WM state was not stable. Circles mark the default modulation strengths used in C. **(E)** The variance at the end of the 10-second delay period is plotted for the model with no modulation at the far left (green; value indicated by dashed line). Improved WM precision (decreased variance) was seen at the end of the delay period under manipulations of recurrent scaling and feedforward to I-cells, though not under feedforward to E-cells. **(F)** Mean firing rate of E-cells during the WM state (same notations as **(E)**), and **(G)** example firing-rate profiles of the WM state with the modulations. Although recurrent scaling and feedforward drive to I-cells both improved WM precision at the behavioral level, they made dissociable predictions at the neural level: recurrent scaling increased firing-rate activity, whereas feedforward drive to I-cells decreased activity. For panels **(E-G)**, the top and bottom rows correspond to the control and disinhibition regimes, respectively.

Table. 1
Demographic Characteristics of Subjects.

HCS and SCZ groups significantly differed in race and paternal education. By design, the groups also differed in IQ scores, participant level of education, PANNS and SAPS/SANS scores.

	Healthy Controls (HCS, n=32)		Patients (SCZ, n = 33)		Significance	
	Mean	**S.D.**	**Mean**	**S.D.**	**T-value/Chi-Square**	**P-value (2-tailed)**
Age (y)	25.51	3.29	28.30	9.40	1.56	0.118
Race (%)	AA: 25 C: 59.38 Asian: 15.63 Mixed: 0		AA: 45.45 C: 42.42 Asian: 3.03 Mixed: 9.09		8.54	0.036*
Gender (% male)	71.9	0.46	78.8	0.42	0.639	0.525
Paternal education (y)	15	2.26	13.21	3.44	2.39	0.020*
Maternal education	14.93	2.92	13.4	3.19	1.94	0.057
Paternal SES	29	12.35	22.59	14.1	1.86	0.067
Maternal SES	26.17	11.94	22.76	12.89	1.05	0.29
Participant's education (years)	16.5	2.26	13.21	2.20	5.82	<0.001***
Handedness (% right)	86.67	34.57	86.67	34.57	0	1
WRAT-3	51.67	5.19	46.5	5.88	3.62	<0.001***
IQ Verbal	121.83	15.45	98.62	19.41	5.12	<0.001***
IQ Non-verbal (Matrix)	114.81	13.38	98.70	15.48	4.03	<0.001***
Medication (CPZ equiv)	NA	NA	307.10	171.60	NA	NA
PANNS Positive	7.53	0.62	20.1	4.91	15.02	<0.001***
PANNS Negative	8.25	1.11	21.04	6.03	12.0	<0.001***
PANNS General	17.03	1.80	38.72	6.70	18.7	<0.001***
Mean SAPS Global	0.055	0.27	2.16	0.99	12.0	<0.001***
Mean SANS Global	0.24	0.37	2.75	0.83	16.25	<0.001***