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Schizophrenia is associated with a pattern of spatial working memory deficits consistent with cortical disinhibition

Martina Starc^{a,b,1}, John D. Murray^{a,c,1}, Nicole Santamauro^a, Aleksandar Savic^{a,d}, Caroline Diehl^{a,b}, Youngsun T. Cho^a, Vinod Srihari^a, Peter T. Morgan^a, John H. Krystal^{a,h}, Xiao-Jing Wang^c, Grega Repovs^{b,1}, Alan Anticevic, Ph.D.^{a,e,f,g,i,*}

^a Department of Psychiatry, Yale University School of Medicine, 300 George Street, New Haven, CT 06511, USA

^b Department of Psychology, University of Ljubljana, Ljubljana, Slovenia

^c Center for Neural Science, New York University, New York, NY 06510, USA

^d University Psychiatric Hospital Vrapce, University of Zagreb, Zagreb 10000, Croatia

^e Abraham Ribicoff Research Facilities, Connecticut Mental Health Center, New Haven, CT 06519, USA

^f Interdepartmental Neuroscience Program, Yale University, New Haven, CT 06520, USA

^g NIAAA Center for the Translational Neuroscience of Alcoholism, New Haven, CT 06519, USA

^h Department of Neurobiology, Yale University, New Haven, CT, USA

ⁱ Department of Psychology, Yale University, 2 Hillhouse Avenue, CT 06520, USA

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ABSTRACT

Schizophrenia is associated with severe cognitive deficits, including impaired working memory (WM). A neural mechanism that may contribute to WM impairment is the disruption in excitation-inhibition (E/I) balance in cortical microcircuits. It remains unknown, however, how these alterations map onto quantifiable behavioral deficits in patients. Based on predictions from a validated microcircuit model of spatial WM, we hypothesized two key behavioral consequences: i) increased variability of WM traces over time, reducing performance precision; and ii) decreased ability to filter out distractors that overlap with WM representations. To test model predictions, we studied $N = 27$ schizophrenia patients and $N = 28$ matched healthy comparison subjects (HCS) who performed a spatial WM task designed to test the computational model. Specifically, we manipulated delay duration and distractor distance presented during the delay. Subjects used a high-sensitivity joystick to indicate the remembered location, yielding a continuous response measure. Results largely followed model predictions, whereby patients exhibited increased variance and less WM precision as the delay period increased relative to HCS. Schizophrenia patients also exhibited increased WM distractibility, with reports biased toward distractors at specific spatial locations, as predicted by the model. Finally, the magnitude of the WM drift and distractibility were significantly correlated, indicating a possibly shared underlying mechanism. Effects are consistent with elevated E/I ratio in schizophrenia, establishing a framework for translating neural circuit computational model of cognition to human experiments, explicitly testing mechanistic behavioral hypotheses of cellular-level neural deficits in patients.

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1. Introduction

Schizophrenia (SCZ) is associated with profound cognitive deficits, such as memory and executive function (Barch and Ceaser, 2012; Kalkstein et al., 2010), which are among the best predictors of vocational and social disability (Green, 2006; Nuechterlein et al., 2011).

Problems with working memory (WM) – the ability to transiently maintain and manipulate information internally – are particularly prominent in SCZ (Forbes et al., 2009; Lee and Park, 2005) and have been proposed as a core cognitive deficit in this illness (Barch and Ceaser, 2012; Goldman-Rakic, 1994; MacDonald et al., 2006; Silver et al., 2003; Van Snellenberg and de Candia, 2009). While SCZ patients show WM deficits across modalities (Quee et al., 2010), spatial WM is particularly amenable for clinical translation as it can be studied across animal (Wang et al., 2013), pharmacological (Driesen et al., 2013), computational modeling (Compte et al., 2000) and patient studies (Driesen et al., 2008) using comparable paradigms. Here we examined specific

* Corresponding author at: Yale University, Department of Psychiatry, 34 Park St., New Haven, CT 06519, USA.

E-mail address: alan.anticevic@yale.edu (A. Anticevic).

¹ Designates equal contributions.

mechanisms of spatial WM deficits based on explicit predictions of a biophysically-based computational WM model (Murray et al., 2014) informed by primate physiology experiments.

Decades of primate and human studies have implicated prefrontal cortex (PFC) neural circuits in WM maintenance and manipulation, which are impaired in SCZ (Anticevic et al., 2013b; Barch and Ceaser, 2012; Metzack et al., 2011). The cellular basis of spatial WM maintenance implicates persistent firing of location-selective PFC pyramidal cells (Funahashi et al., 1989)—extensively characterized by animal electrophysiology (Rao et al., 2000; Wang et al., 2013) and computational modeling (Compte et al., 2000; Durstewitz et al., 1999; Durstewitz and Seamans, 2002; Wang, 2006; Wang, 2010; Wang et al., 2004). The models propose that WM is supported by the interplay between recurrent excitation (E) among pyramidal neurons (which sustains persistent activity over the delay) and lateral inhibition (I) mediated by interneurons (which stabilizes WM representations and reduces the impact of external distraction) (Compte et al., 2000; Murray et al., 2014; Wang et al., 2004). Specific alterations in optimal E/I balance disrupt the ability to represent information and shield WM from interference (Rao et al., 2000). One such potential alteration—disruption of inhibitory interneurons, leading to cortical disinhibition—has been implicated in SCZ neuropathology (Lewis et al., 2005; Marin, 2012). It remains unknown, however, how such cellular hypotheses map onto quantifiable behavioral WM deficits. Here we tested the behavioral consequences of altered E/I balance on spatial WM performance in SCZ.

Biophysically realistic computational modeling offers one strategy to quantify the impact of altered E/I balance on WM (Anticevic et al., 2013a; Anticevic et al., 2015; Murray et al., 2014). The consequences of cortical disinhibition on WM are well-characterized by a spiking local circuit model comprised of E- and I-cells (Murray et al., 2014). E-cells interact through horizontal connections mediating recurrent excitation via N-methyl-D-aspartate receptors (NMDAR) and a pool of I-cells mediates feedback synaptic inhibition. Prior work modeled cortical disinhibition by reducing NMDAR conductance for E-I connections (Kotermanski and Johnson, 2009), thought to occur in SCZ by the well-established NMDAR hypo-function hypothesis (Anticevic et al., 2012a; Krystal et al., 2003a; Macdonald and Chafee, 2006).

We used this model architecture to derive testable qualitative behavioral predictions generated by NMDAR hypo-function on I-cells. First, the model predicted that following disinhibition, WM representational fields are broadened, resulting in increased random drift over time. This effect was observed behaviorally as a reduction in WM precision over longer delays. Second, the model predicted distorting effects of intervening distractors on WM, whereby under disinhibition, a broader WM representation exhibits a wider window in which distractors can interfere with WM (Murray et al., 2014). Finally, the model predicted that both increased response variability and increased distractor sensitivity stem from a shared underlying mechanism—altered E/I balance. We tested these three model-derived hypotheses in patients diagnosed with SCZ. Collectively, this ‘computational psychiatry’ study translates a neural circuit computational model of cognition to test behavioral hypotheses of cellular-level neural deficits in SCZ patients.

2. Methods

2.1. Subjects

We recruited $N = 27$ SCZ patients from outpatient clinics of the Department of Psychiatry, Yale University and $N = 28$ healthy comparison subjects (HCS) from the local community (Table 1). Subjects were independently diagnosed by two trained clinicians using the Structured Clinical Interview (SCID) for DSM-IV (First et al., 2001). All subjects provided informed consent approved by Yale Institutional Review Board. Patients met DSM-IV diagnostic criteria for SCZ or schizoaffective disorder, but no other Axis I diagnosis or drug abuse/dependence at the time

of recruitment. Prior and current nicotine and alcohol use was permitted. HCS met the following inclusion criteria: i) no current or lifetime Axis I disorder (determined by a trained PhD-level clinician); and ii) no history of psychotic, mood or other Axis I disorders in first-degree relatives (reported by detailed family history). Subjects were excluded if they had: i) history of other neurological conditions (e.g. epilepsy, migraine, head trauma, loss of consciousness); ii) any MRI contraindications; or iii) any concomitant major medical disorder. HCS were demographically matched to SCZ patients. However, groups differed in education attainment and measures of verbal and non-verbal intelligence, as expected in severe mental illness (Glahn et al., 2006) (Table 1). Critically, adjusting for these variables did not alter results (see Supplement).

2.2. Current symptoms & medication

Symptom severity was evaluated using the Scale for Assessment of Positive and Negative Symptoms (SAPS/SANS) (Andreasen, 1983b) and the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987). 85% of patients (23/27) were receiving antipsychotics, which we converted to chlorpromazine (CPZ) equivalents (Andreasen et al., 2010) (Table 1). None of the identified effects correlated with CPZ equivalents and did not change when we co-varied for medication dose (see Supplement).

2.3. Computational model

Full details of the computational model implementation were reported previously (Murray et al., 2014). For the purposes of the current experimental predictions we modeled a cortical circuit that performs spatial WM through stimulus-selective persistent activity. The circuit contains recurrently connected E pyramidal cells and I interneurons. Pyramidal cells are tuned to angular location. Stimulus inputs transiently excite a corresponding subset of E-cells, and a persistent activity pattern encodes stimulus location through the delay. Cortical disinhibition was implemented through a reduction of excitatory NMDA conductance on interneurons (G_{EI}), a site implicated in the pathology of SCZ (Anticevic et al., 2012a; Belforte et al., 2010; Krystal et al., 2003b). We used the population vector approach to decode the behavioral report location from the neural WM activity pattern. We characterized two aspects of model performance: i) time-dependent decay of WM precision by computing the across-trial variability of the decoded location as a function of delay duration. ii) behavioral impact of external distractors on WM report. Distractors were identical to the initial cue, with the same intensity and duration but with a different stimulus position (Fig. 2D).

2.4. Experimental design

Subjects completed two delayed spatial WM paradigms, designed to mimic primate physiology experiments (Goldman-Rakic, 1995) and the implemented computational model architecture (Compte et al., 2000). The tasks manipulated: i) delay period duration (testing if the SCZ group exhibits greater WM response variability as a function of delay duration), and ii) distance between the WM cue and distractor presented during the delay period (testing if the SCZ group exhibits a differential response bias in the direction of the distractor across two distractor distances, Fig. 1; see Supplement for comprehensive detail). Subjects also completed a control ‘motor’ task to verify that differences between groups are not driven exclusively by lower motor skill in patients. Subjects were instructed to keep their eyes fixed on the middle of the screen throughout the task and were monitored for compliance by the experimenter (see Limitations for considerations surrounding eye tracking). Response expectations were controlled for by insuring that the number of trials decreased with delay duration (from 60 to 20; see Supplement for complete details).

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