Title

Refining the Empirical Constraints on Computational Models of Spatial Working Memory in Schizophrenia

Journal

Biological Psychiatry Cognitive Neuroscience and Neuroimaging, 5(9)

ISSN

2451-9022

Authors

Gold, James M
Bansal, Sonia
Anticevic, Alan
et al.

Publication Date

2020-09-01

DOI

10.1016/j.bpsc.2020.05.003

Peer reviewed

HHS Public Access

Author manuscript

Biol Psychiatry Cogn Neurosci Neuroimaging. Author manuscript; available in PMC 2022 March 16.

Published in final edited form as:

Biol Psychiatry Cogn Neurosci Neuroimaging. 2020 September ; 5(9): 913–922. doi:10.1016/j.bpsc.2020.05.003.

Refining the empirical constraints on computational models of spatial working memory in schizophrenia

James M. Gold[1], **Sonia Bansal**[1], **Alan Anticevic**[2], **Youngsun T. Cho**[2,3], **Grega Repovš**[4], **John D. Murray**[2], **Britta Hahn**[1], **Benjamin M. Robinson**[1], **Steven J. Luck**[5]

[1]Maryland Psychiatric Research Center, Department of Psychiatry, University of Maryland School of Medicine, Baltimore, MD

[2]Department of Psychiatry, Yale University School of Medicine, New Haven, CT

[3]Child Study Center, Yale University School of Medicine, New Haven, CT

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

[5]Center for Mind & Brain and Department of Psychology, University of California, Davis, CA

Abstract

Background.—Impairments in spatial working memory (sWM) have been well-documented in schizophrenia. Here we provide a comprehensive test of a microcircuit model of WM performance in schizophrenia, which predicts enhanced effects of increasing delay duration and distractors based on a hypothesized imbalance of excitatory and inhibitory processes.

Methods: Model predictions were tested in 41 clinically stable people with schizophrenia (PSZ) and 32 healthy control subjects (HCS) performing a spatial WM task. In one condition, a single target location was followed by delays of 0, 2, 4, or 8 seconds. In a second condition, distractors were presented during the 4-second delay interval at 20, 30, 40, 50, or 90 degrees from the original target location.

Results: PSZ showed less precise sWM representations than HCS, and the rate of memory drift over time was greater in PSZ than in HCS. Relative to HCS, the spatial recall responses of PSZ were more repelled by distractors presented close to the target location and more attracted by distractors presented far from the target location. The degree of attraction to distant distractors was correlated with the rate of memory drift in the absence of distractors.

Conclusions.—Consistent with the microcircuit model, PSZ exhibited both a greater rate of drift and greater attraction to distant distractors relative to HCS. These two effects were correlated, consistent with the proposal that they arise from a single underlying mechanism. However, the repulsion effects produced by nearby distractors were not predicted by the model and thus require an updated modeling framework.

Correspondence concerning this article should be addressed to: James M. Gold, MPRC, PO Box 21247, Baltimore Maryland 21228, 410 402 7871, jgold@som.umaryland.edu.

Keywords

Schizophrenia; working memory; computational model; distractor effects; E-I balance; precision

1. INTRODUCTION

Beginning with Park and Holzman (1, 2), numerous studies of spatial working memory (sWM) have documented that PSZ have substantial deficits when asked to report a single spatial location after a brief delay period (3). In some (but not all) studies, the impairment is present at short delays and is amplified by increasing the delay interval, suggesting impairments in both initial encoding and maintenance of sWM representations (4–7). Multiple fMRI studies report abnormal responses in PSZ in prefrontal and parietal areas that support sWM (8–10), in line with pharmacological studies (11). Although the behavioral and imaging evidence of impairment is robust, the specific neural and computational mechanisms remain underspecified.

Anticevic, Murray and colleagues developed a computational modeling approach (See Figure 1) that proposes a possible mechanism to explain sWM deficits in PSZ (7,12,13), hypothesizing an alteration in the balance of excitatory and inhibitory (E-I) processes in cortical microcircuits characterized by disinhibition (11). This work builds on a spiking neural network model where sWM performance involves an interaction between the recurrent excitation of pyramidal neurons and lateral inhibition by interneurons (14–16). The recurrent excitation is needed to sustain WM representations over delay intervals, while the inhibition serves to sculpt the precision of WM representations, reduce drift over time, and minimize the impact of distractors.

Such models are of particular interest in schizophrenia because there is evidence that the illness involves a compromise of inhibitory interneuron function, possibly as a result of NMDA receptor hypofunction (11, 16–19). According to the E/I imbalance model, decreased inhibitory function should have two specific impacts on sWM performance: 1) greater loss of sWM precision with longer delay intervals; and 2) increased vulnerability to the impact of distractor stimuli presented close to the original representation. Per model predictions, decreased inhibition allows the excitatory processes that represent the target location to spread to neighboring neuronal populations, resulting in broadening of the target representation over time. The model suggests that vulnerability to distractor stimuli arises from the same underlying mechanism: a broader sWM representation is more likely to overlap with the neuronal representation of a nearby distractor. This overlap causes the target sWM representation to shift towards the distractor representation. However, this attraction can occur only when the distractor representation overlaps the target representation. In a moderately powered initial test of model predictions (N = 27 PSZ, 28 controls), Starc et al (7) reported that PSZ showed a steeper loss of precision with increasing delay, as well as a significant correlation between memory drift and vulnerability to distractors. However, as noted by Starc et al, the distractor results were not fully consistent with model predictions in that PSZ showed attraction towards distractors that were distant from the target but not to distractors positioned close to the target. Therefore, an important knowledge gap remains –

namely to comprehensively test the predictive limits of the current microcircuit model in a well-powered sample, which can inform subsequent model expansion.

The current experiment was designed to provide a more definitive test of model predictions, which was not possible with the task used by Starc et al (7) because it was designed for use in fMRI. We made several key task design improvements: First, we included distractors at a broad set of distances from the target in order to parametrically map distractor effects. Second, we employed eye tracking to ensure central fixation was maintained when targets were presented, thus controlling for the possibility that eye movements were used as a means of maintaining target position. Third, we excluded the longest delays (up to 20 seconds), which were included to match the needs of fMRI and which may result in errors from mind-wandering rather than pure loss of sWM precision (20). Finally, we shortened the target presentation to 200 ms to minimize eye movements and longer-term encoding strategies. Guided by modeling results, we tested delays of 0 to 8 seconds, which should be adequate to evaluate changes in precision over time while minimizing mind-wandering confounds. This paradigm was designed to enable a conclusive empirical test of the Murray-Anticevic E-I model. Critically, the study was conducted by a laboratory that did not participate in the original model development to ensure an independent and rigorous test of the original model predictions.

2. METHODS

2.1. Participants

Forty-one people with a diagnosis of schizophrenia or schizoaffective disorder (collectively referred to as PSZ) were recruited from the Maryland Psychiatric Research Center (MPRC) and other local clinics. Material from medical records and the results of the Structured Clinical Interview for (DSM)-IV-TR Axis 1 Disorders (21) were combined to make a diagnosis based on the Diagnostic and Statistical Manual of Mental Disorders IV-TR (22) at a consensus conference.. All PSZ were clinically stable outpatients who had been receiving the same medications, at the same dose, for at least 4 weeks prior to study participation. In terms of medication use, clozapine was the most frequently used antipsychotic either as monotherapy (N=11) or combined with a second antipsychotic (N=6). Six PSZ were taking a first-generation antipsychotic. Thirteen PSZ were receiving monotherapy with a second generation antipsychotic other than clozapine, while 5 were taking two antipsychotics other than clozapine. Antidepressants were widely used (N=21) as were anxiolytics (N=14). In addition, 6 PSZ were taking an anticholinergic and 10 were taking a mood stabilizer.

Healthy controls (HCS) (N=32) were recruited via online advertisements and local bulletin boards. They were screened using the Structured Clinical Interview for DSM-IV-TR Axis 1 Disorders (SCID-I; (21)) and Axis II Personality Disorders (SIDP-R; (23)). All had no current Axis I disorder or Axis II schizophrenia-spectrum disorder, neurological disorder, or cognitively-impairing medical disorder, and all denied a lifetime history of psychosis or any family history of psychotic disorders in first-degree relatives.

After complete description of the study, written informed consent was obtained. The protocol was approved by the Institutional Review Board of the University of Maryland Baltimore.

2.2. Clinical Assessments

We administered the Brief Psychiatric Rating Scale (BPRS, 24) to quantify overall symptom severity, and the Scale for the Assessment of Negative Symptoms (SANS; 25), to quantify negative symptoms. In addition, all subjects received the Wechsler Test of Adult Reading (26), which provides an estimate of premorbid intellectual ability.

2.3. Apparatus.

The task was presented using E-Prime version 1.0 (Psychology Software Tools, Inc.) on a HP ZR2440w monitor with a 60 Hz refresh rate at a viewing distance of 100 cm. The measured monitor lag was subtracted from RTs. An eye tracker (Eyelink1000 v4.31, SR Research Ltd., Mississauga, Ontario) recorded eye movements to track gaze stability during the fixation period. Manual responses were collected using a computer mouse.

2.4. Task Design.

The experimental task (Figure 2) was based on the design by Starc et al. (7), which was developed to mimic primate physiology experiments (27) and the ring-shaped spatial configurations commonly used in computational microcircuit models (14). One condition manipulated the delay duration and another included distractors at varying distances from the target. For the *delay condition*, participants were asked to remember the position of a target circle that was presented at one of 20 pseudo-randomly chosen angles along a notional circle that had a radius of approximately 9.5° degrees of visual angle. Subjects began a trial by establishing fixation on a central cross. Then a small target circle (approximately 1.8°) was displayed for 200ms, followed by a delay of 0, 2, 4, 8 seconds. Subjects were instructed to maintain fixation during the delay interval. At the end of the delay period, the fixation cross disappeared indicating that it was time to mouse-click on the remembered location. A total of 120 trials were presented, 30 at each delay interval (randomly intermixed), divided into 3 blocks of 40 trials.

The *distractor condition* was identical except that the delay interval was always 4 seconds long and a distractor circle (a 1.8° red circle) appeared 1.3 to 2.3 seconds after the offset of the target. Distractors were positioned on the ring of possible target locations at an angular offset of 20, 30, 40, 50, or 90 degrees from the original target position. Fifty trials per distractor position and 50 trials with no distractors were presented in random sequence, for a total of 300 trials, divided into 10 blocks of 30 trials each. The delay and distractor blocks were administered in random order.

2.5. Analyses

Responses that were displaced more than 90° from the target location (< 1% of trials) were excluded from analyses as these were likely to reflect lapses of attention. Our main sWM accuracy measure was the standard deviation (SD) of the absolute angular response error across trials as an assay of the trial-by-trial memory variability (i.e., the imprecision of

the memory). Response error was defined as the number of degrees around the circle of possible stimulus locations between the center of the target and the reported location. For the delay task, we quantified the slope of the function relating the SD to delay duration, which provides a measure of the sWM drift rate over time. For the distractor task, the sign of the error was negative if the error was biased away from the distractor location and positive if it was biased toward the distractor location.

The data from the delay condition were analyzed in a 2 × 4 mixed-design ANOVA, including *Group* (PSZ, HCS) as a between-subjects factor and *Delay Duration* (0, 2, 4 and 8 s) as a within-subjects factor. The data from the distractor condition were analyzed in a 2 × 5 mixed-design ANOVA with *Distractor Distance* (20°, 30°, 40°, 50°, 90°) as a within-subjects factor and *Group* (PSZ, HCS) as a between-subjects factor. The Greenhouse–Geisser correction was used when the sphericity assumption was not met.

Due to the observed group differences in years of education and marginal differences in age between the two groups, we used these scores as covariates in supplementary analyses. These ANCOVAs yielded the same effects as the ANOVAs, so we report the ANOVAs here. We used Spearman correlations to examine the relationships amongst WM performance measures and with other clinical measures given modest sample size. All statistical tests employed a two-tailed significance threshold of $\alpha<0.05$ and were performed using MATLAB and JASP software (JASP Version 0.8.5; jasp262 stats.org).

3. RESULTS

Background demographic and cognitive features are shown in Table 1. The groups had similar age, gender and ethnicity distributions and similar parental education. Table 2 contains the statistical test results for the experimental tasks, including *p* values and effect sizes. Consequently, these statistics will not be provided in the text.

3.1. Effects of delay duration on spatial WM performance

We first examined the data from the *Delay* condition to assess whether sWM representations were less precise (i.e., more spatially variable) in PSZ and whether this loss of precision was amplified over increasing delays. Precision can be seen in the spread of single-trial responses (Figure 3A) and in the SD across trials (Figure 3B). The single-trial responses have been rotated as if the target was always at the 3 o'clock position. Response variability increased with delay duration in both groups, which was corroborated by a significant main effect of *Delay Duration*. PSZ had greater variability than HCS at all delay durations (significant main effect of *Group*). PSZ exhibited a greater effect of *Delay Duration* on SD than did HCS (significant *Delay Duration* × *Group* interaction). The effect size of this group difference grew linearly with increasing delay. This result was corroborated by an analysis of the slope of the SD increase over time. The slope in PSZ (0.40° per second) was significantly larger than in HCS (0.24° per second); $t(72) = 3.40$, $p= 0.0011$, (Figure 3B–C). This increase is also captured in the overall drift rate, which differed significantly between groups (HCS, 0.24 ± 0.12; PSZ, 0.41 ± 0.24; $t =3 .83$, $p<0.001$, Cohen's $d = 0.866$, Figure 3D).

3.2 Effects of distractor position on spatial WM performance

Figure 4A shows the single-trial responses for each distractor distance in the distractor condition. The single-trial data have been rotated as if the target was always at the 3 o'clock position and as if the distractor was always counterclockwise relative to the target. Four important results emerged from this analysis. First, at the larger distractor offsets, a portion of the single-trial responses in both groups were biased in the direction of the distractor. Second, this attraction bias was unlikely to be a result of confusion about which item was the target, because most of these responses fell between the target and the distractor. Confusions, in contrast, would have led to a set of responses distributed symmetrically around the distractor. Third, a bias *away* from the distractor (repulsion) can be seen in the 20° condition in PSZ. That is, in this condition, a cluster of responses can be seen directly opposite to the location of the distractor. Fourth, as in the delay condition, overall response variability was greater in PSZ than in HCS (Figure 4B).

The difference in response variability (SDs, displayed in Figure 4B) was statistically significant (main effect of *Group*). Response variability was also somewhat increased in the 90° distractor trials relative to other distractor distances, but this effect did not reach significance (main effect of *Distractor Distance*, p=0.06). Further, we did not observe a significant *Distractor Distance* × *Group* interaction.

We also examined the angular response error relative to the distractor location (Figure 4C), which indicates the extent to which the response was attracted toward the distractor (positive bias) or repelled away from the distractor (negative bias). This measure clearly shows attraction of responses toward the distractor for the 40°, 50° and 90° distractor distances in both groups. It also shows repulsion away from the distractor for the 20° distance in PSZ but not in HCS. This pattern led to a main effect of *Distractor Distance* and a significant *Distractor Distance* × *Group* interaction. Comparisons between PSZ and HCS at each distractor distance showed that PSZ exhibited significantly more repulsion than HCS at 20°, whereas they exhibited significantly more attraction than HCS at 50° and 90°.

3.3. Correlations between working memory measures

Both the increased drift over time (Figure 3D) and the increased distractor attraction effects (Figure 4C) were hypothesized to arise from the same mechanism in the computational model. This leads to the prediction that the sWM drift rate in the delay task (the slope of the function relating SD to the delay duration) will be correlated with the magnitude of the response bias toward the distractor (aggregated across distractor distances > 20°) in the distractor task. As seen in Figure 5 (top) and Table 3, there was a robust correlation in PSZ (rho=0.52, p<.001), but not in HCS, perhaps due to limited variance in the HCS.

As seen in Figure 5 (bottom), the bias at the larger distractor distances (>20°) correlated positively with the bias at the 20° position (for both groups: rho=0.58, p<0.001). Positive bias values mean attraction toward the distractor, so this positive correlation indicates that individuals who exhibited higher levels of attraction to the far distractors also exhibited higher levels of attraction to the 20° distractors (i.e., *less* repulsion by the 20° distractors). The direction of this correlation appears to provide evidence against the possibility that

a single mechanism produces both repulsion by nearby distractors and attraction toward distant distractors, which would have produced a negative correlation (i.e., greater positive bias for the distant distractors would have been associated with a greater negative bias for the 20° distractors). Instead, it may indicate that an attraction effect is present at all distractor distances (producing a positive correlation between the bias at 20° and the bias at greater distances), and a separate repulsion effect is superimposed on this attraction effect for nearby distractors (producing the overall repulsion at 20° in PSZ). As shown in Supplementary Figure S1, the bias at 20° was not significantly correlated with the drift rate in either group (PSZ: rho= 0.20; HCS: rho= 0.12).

3.4. Clinical correlations.

Table 3 shows correlations between our sWM summary measures and each of our clinical and medication measures, and Supplementary Figure S1 shows each of the scatterplots. The sWM measures were modestly (but not significantly) correlated with positive symptoms and were uncorrelated with negative symptoms. Chlorpromazine dose (28) positively correlated with the bias toward the distractor and the drift rate. A higher dose was associated with greater attraction at both the close and far distractor distances, even though PSZ exhibited an overall repulsion at 20°. That is, PSZ showed more repulsion (less attraction) than HCS at 20°, but within PSZ higher medication levels were associated with less repulsion (more attraction). This effect suggests that a single mechanism produces attraction at all distances (and is associated with medication dose), whereas another mechanism produces repulsion at close distances (and is not associated with medication dose). Note, however, that medication dosage was also positively associated with positive symptom levels (presumably reflecting symptom-based dosage decisions), making it difficult to disentangle cause and effect. We did not observe any correlations that approached significance between the three measures of sWM performance and BPRS negative and disorganization symptoms nor with SANS total scores.

4. DISCUSSION

The present data replicate and extend previous findings of Starc et al. (7), providing evidence that spatial WM representations are less precise and more impacted by the passage of time in PSZ than in HCS. We also confirmed that distractors have a greater impact in PSZ than in HCS. These are important conclusions for understanding the neural mechanisms of sWM impairments in PSZ, and the present study can draw them with greater certainty than most previous studies because of our larger sample size and our ability to rule out eye movements, lapses of attention, and target-distractor confusions as sources of the observed effects.

A meta-analysis published in 2005 concluded that there was no evidence that the WM impairment in PSZ increased as the delay period increased (29). Indeed, the MPRC group previously published evidence for similar levels of impairment over differing delays using a color WM paradigm with memory arrays of 3 or 4 items (30). However, some paradigms and analytic procedures may be more sensitive than others for detecting delay-dependent effects. For example, because the color WM data from the MPRC group were obtained

with near-capacity set sizes, the data contained a large number of guesses, making it more difficult to reliably estimate the precision of the WM representations. Tasks requiring the reporting the exact value of a single to-be-remembered stimulus are optimal for evaluating the precision of WM representations (as in the present study). Given the present results, those of Starc et al.(7), and others (4,6), it now seems safe to conclude that sWM impairments in PSZ are magnified at longer delay intervals. These effects are fully consistent with the altered E-I balance framework proposed by Murray and Anticevic (12).

The present results also replicate and extend the distance-dependent effects of distractors reported by Starc et al. We also observed greater attraction in PSZ than in HCS towards distractors presented at the two greatest distances from the target location (50° and 90°). We also replicated the finding of greater repulsion away from distractors presented close to the target location (20°) in PSZ relative to HCS. Starc et al (2017) saw a similar trend at 20° and noted that this result was difficult to account for in their model.

In the microcircuit model, a single mechanism (reduced E/I balance) produces both the increased memory drift and the greater distractor attraction in PSZ. This prediction was supported by a robust correlation between the drift rate and the magnitude of distractor attraction in PSZ. Notably, this correlation was not significant in HCS, but that may simply mean that the E/I balance is relatively consistent across healthy individuals.

The model also predicts that the attraction bias should be more potent for distractor locations that are in close proximity to the target, where the neural representations of the target and distractor locations maximally overlap. The data seen in Figure 3 contradict this model-based prediction as we saw repulsion from the nearest distractors (as in Starc et al (2017)) and attraction towards the most distal distractors, which involve the least feature overlap with the target. We consider this enhanced proximal repulsion in PSZ to be the most challenging result as current computational approaches do not provide an account for this phenomenon.

The fact that both studies observed an increased repulsion at 20° in PSZ enhances confidence that this effect is a real phenomenon. Further, the MPRC group has observed similar enhanced repulsion effects in PSZ in two other sWM paradigms (31). This repulsion effect does not appear to reflect the same mechanism that produces distraction at greater target-distractor distances. The degree of bias at 20° was correlated with the degree of bias at larger separations, but the direction of this correlation was the opposite of what would have been expected if a single mechanism produced both the repulsion at 20° and the attraction at greater distances. Moreover, medication dosage was positively associated with both greater attraction at the larger distances and less repulsion (greater attraction) at 20°. Finally, the drift rate was correlated with the attraction at greater distances (in PSZ) but not with the repulsion at 20°.

Repulsion is naturally explained by short-range lateral inhibition between representations (32), so it is puzzling that repulsion would be greater in PSZ than in HCS. However, a different and yet to be explained repulsion mechanism may be operating at the level of cortical circuits supporting sWM. This robust yet surprising repulsion finding will be an

important target for future modeling and empirical studies to help establish if in fact is stems from a uniquely dissociable mechanism from the other sWM effects accounted by the model.

These results highlight advantages of computational models but also bring into focus aspects of the model that need to be revisited to account for the repulsion effect. We argue that pinpointing the model's limits and attempting to rigorously falsify its predictions is critical for making progress. The value of explicit but simplified biophysical mechanistic models is that they lead to highly specific predictions that can be tested, with the results feeding back to further model development and subsequent empirical testing. The E-I imbalance disinhibition framework is valuable for precisely this reason. It is built upon our current understanding of the neurobiology of schizophrenia and lends itself to precise empirical tests that can be back-translated. Here we found empirical evidence of repulsion from near distractors that does not map onto current models of the microcircuitry of WM. This is not a failure of the model-based approach; instead, it is a clear signal that will guide future model development.

This study has a number of limitations. One might expect that a measure sensitive to a central underlying neurobiological abnormality should relate to the cardinal symptoms of the illness. We did not observe any such relationships. We studied medicated PSZ, most ill for many years. It would be important to study measures of E-I balance in unmedicated, first episode cases to evaluate the roles of chronicity and medication status. Our results involving medication dose and attraction effects and drift rate are confounded by the clinical features that resulted in the use of higher medication doses.

In conclusion, these data identify four key features of sWM impairments in PSZ: 1) poorer precision, even at very short delays; 2) greater drift over time; 3) greater attraction toward distant distractors; and 4) greater repulsion away from nearby distractors. The first three of these confirm the predictions of a microcircuit model of sWM disinhibition, demonstrating the predictive power of the model. The fourth effect cannot be accommodated by the model in its current form, suggesting the presence of an additional mechanism that will be an important target for future research. These results illustrate the value of empirical research to guide further development of biophysically grounded models of cognitive dysfunction in mental illness.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments:

This study was made possible by NIMH grant MH065034 to JMG and SJL.

We gratefully acknowledge the efforts of Leeka Hubzin and Sharon August in data collection.

Disclosures:

JMG receives royalty payments from Vera Sci. AA consults, holds equity and has received funding from Blackhorn Therapeutics. All other authors report no biomedical financial interests or potential conflicts of interest.

REFERENCES

1. Park S, Holzman PS (1992): Schizophrenics show spatial working memory deficits. Arch Gen Psychiatry 49(12): 975–982. [PubMed: 1449384]
2. Minor K, Park S (1999): Spatial working memory: absence of gender differences in schizophrenia patients and healthy control subjects. Biol Psychiatry 46(7): 1003–1005. [PubMed: 10509184]
3. Piskulic D, Olver JS, Norman TR, Maruff P (2007): Behavioural studies of spatial working memory dysfunction in schizophrenia: a quantitative literature review. Psychiatry Res 150(2): 111–121. [PubMed: 17292970]
4. Badcock JC, Badcock DR, Read C, Jablensky A (2008): Examining encoding imprecision in spatial working memory in schizophrenia. Schizophr Res 100(1–3): 144–152. [PubMed: 17804202]
5. Tek C, Gold J, Blaxton T, Wilk C, McMahon PR, Buchanan RW (2002): Visual perceptual and working memory impairments in schizophrenia. Arch Gen Psychiatry 59(2): 146–153. [PubMed: 11825136]
6. Mazhari S, Badcock JC, Waters FA, Dragović M, Badcock DR, Jablensky A (2010): Impaired spatial working memory maintenance in schizophrenia involves both spatial coordinates and spatial reference frames. Psychiatry Res 179(3): 253–258. [PubMed: 20493553]
7. Starc M, Murray JD, Santamauro N, Savic A, Diehl C, Cho YT, Srihari V, et al. (2017): Schizophrenia is associated with a pattern of spatial working memory deficits consistent with cortical disinhibition. Schizophr Res 181: 107–116. [PubMed: 27745755]
8. Lee J, Folley BS, Gore J, Park S (2008): Origins of spatial working memory deficits in schizophrenia: an event-related FMRI and near-infrared spectroscopy study. PLoS One 3(3): e1760. [PubMed: 18335036]
9. Driesen NR, Leung HC, Calhoun VD, Constable RT, Gueorguieva R, Hoffman R (2008): Impairment of working memory maintenance and response in schizophrenia: functional magnetic resonance imaging evidence. Biol Psychiatry 64(12): 1026–1034. [PubMed: 18823880]
10. Anticevic A, Repovs G, Barch Dm. (2013) Working memory encoding and maintenance deficits in schizophrenia:neural evidence for activation and deactivation abnormalities. Schizophre Bull 39 (1) 168–78.
11. Anticevic A1, Gancsos M, Murray JD, Repovs G, Driesen NR, Ennis DJ, Niciu MJ, Morgan PT, Surti TS, Bloch MH, Ramini R, Smith MA, Wang XJ, Krystal JH, 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. 2012 Oct 9;109(41):16720–5. [PubMed: 23012427]
12. 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 cortical working memory model. Cereb Cortex 24(4): 859–872. [PubMed: 23203979]
13. Krystal JH, Anticevic A, Yang GJ, Dragoi G, Driesen NR, Wang XJ, Murray JD (2017): Impaired tuning of neural ensembles and the pathophysiology of schizophrenia: a translational and computational neuroscience perspective. Biol Psychiatry 81(10): 874–885 [PubMed: 28434616]
14. Compte A, Brunel N, Goldman-Rakic PS, Wang XJ (2000): Synaptic mechanisms and network dynamics underlying spatial working memory in a cortical network model. Cereb Cortex 10(9): 910–923. [PubMed: 10982751]
15. Durstewitz D, Seamans JK, Sejnowski TJ (2000): Neurocomputational models of working memory. Nat Neurosci 3 Suppl: 1184–1191. [PubMed: 11127836]
16. Wang M, Yang Y, Wang CJ, Gamo NJ, Jin LE, Mazer JA, et al. (2013): NMDA receptors subserve persistent neuronal firing during working memory in dorsolateral prefrontal cortex. Neuron 77(4): 736–749. [PubMed: 23439125]
17. Lisman JE, Coyle JT, Green RW, Javitt DC, Benes FM, Heckers S, Grace AA (2008): Circuit-based framework for understanding neurotransmitter and risk gene interactions in schizophrenia. Trends Neurosci 31(5): 234–242. [PubMed: 18395805]
18. Driesen NR, McCarthy G, Bhagwagar Z, Bloch MH, Calhoun VD, D'Souza DC (2013): The impact of NMDA receptor blockade on human working memory-related prefrontal function and connectivity. Neuropsychopharmacology 38(13): 2613–2622. [PubMed: 23856634]

19. Dienel SJ, Lewis DA (2018): Alterations in cortical interneurons and cognitive function in schizophrenia. Neurobiol Dis pii: S0969-9961(18)30199-2. doi: 10.1016/j.nbd.2018.06.020. [Epub ahead of print]
20. Zhang W, Luck SJ (2009): Sudden death and gradual decay in visual working memory. Psychol Sci 20(4): 423–428. [PubMed: 19320861]
21. First MB, Spitzer RL, Miriam G, Williams JBW (2002): Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Research Version, Non-Patient Edition (SCID-I/NP). New York: Biometrics Research, New York State Psychiatric Institute.
22. American-Psychiatric-Association, ed. (2000): Diagnostic and Statistical Manual of Mental Disorders, 4th, text revision ed. Washington, DC: American Psychiatric Association.
23. Pfohl B, Blum N, Zimmerman M, Stangl D (1989): Structured Interview for DSM-III-R Personality Disorders-Revised (SIDP-R). Iowa City, IA: University of Iowa.
24. Overall JE, Gorham DR (1962): The brief psychiatric rating scale. Psychol Rep 10: 799–812.
25. Andreasen NC (1984): The Scale for the Assessment of Negative Symptoms (SANS). Iowa City: University of Iowa.
26. Wechsler D (2001): Wechsler Test of Adult Reading. San Antonia, TX: The Psychological Corporation.
27. Goldman-Rakic PS (1995): Cellular basis of working memory. Neuron 14: 477–485. [PubMed: 7695894]
28. 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 67:255–262. [PubMed: 19897178]
29. Lee J, Park S (2005): Working memory impairments in schizophrenia: a meta-analysis. J Abnorm Psychol 114(4): 599–611 [PubMed: 16351383]
30. Gold JM, Hahn B, Zhang W, Robinson BM, Kappenman ES, Beck VM, Luck SJ (2010): Reduced capacity but spared precision and maintenance of working memory representations in schizophrenia. Arch Gen Psychiatry 67(6): 570–577. [PubMed: 20530006]
31. Bansal* S, Bae* GY, Frankovich K, Robinson B, Leonard C, Gold J & Luck S (in submission). Increased repulsion of working memory representations in schizophrenia. * = co-first author
32. Blakemore C, Carpenter RHS, & Georgeson MA (1970). Lateral Inhibition between Orientation Detectors in the Human Visual System. Nature, 228, 37–39 [PubMed: 5456209]

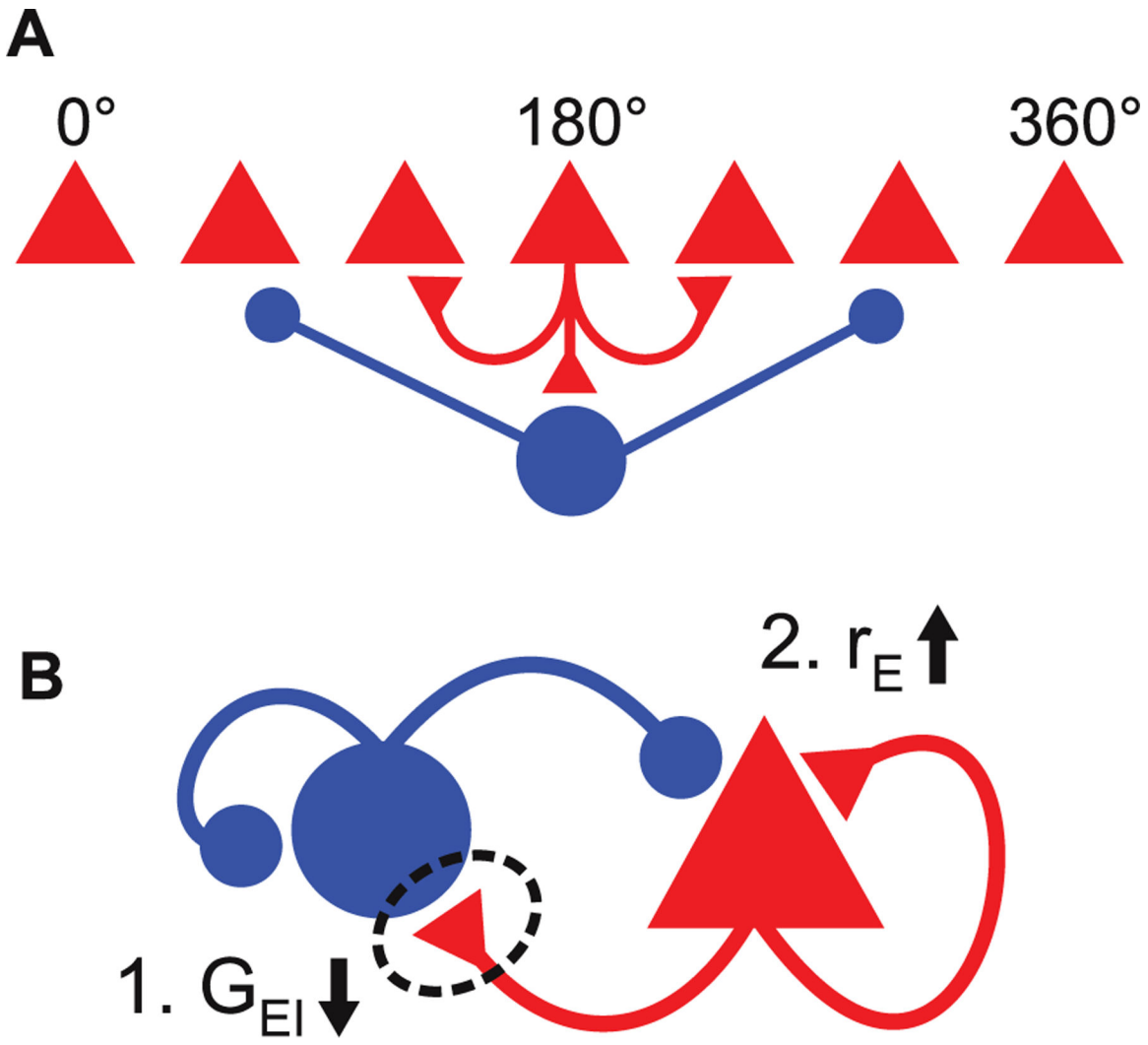

Figure 1.
Schematic illustration of the computational model.

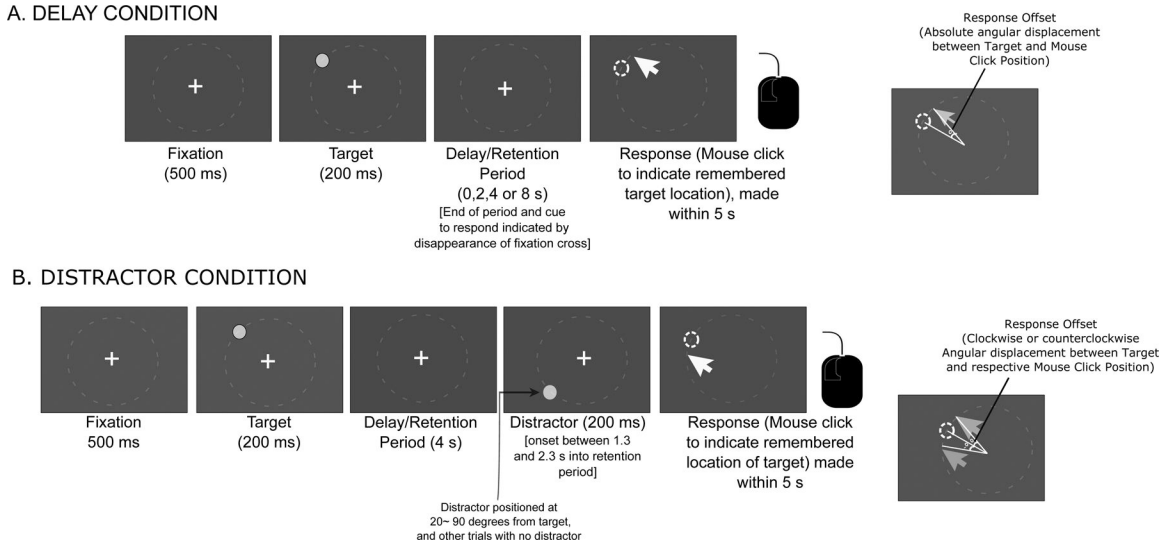

Figure 2. Task conditions.

A. Delay condition. Subjects used a mouse click to indicate remembered target location. B. Distractor condition. Distractors were presented 20–90 degrees from the target location.

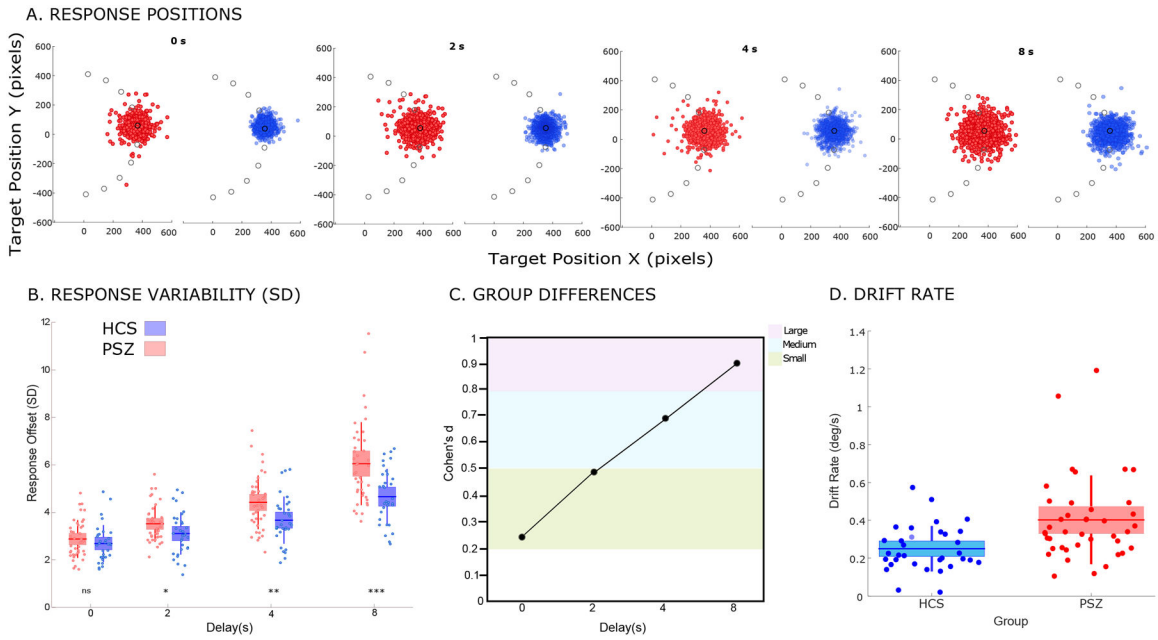

Figure 3. Effects of delay on the precision of spatial WM.

Panel A shows the positions of all responses with all targets rotated to appear at the 3 o'clock position. Responses drift over increasing delays but remain centered around the target location. B. Average standard deviation of response errors. These errors increased in magnitude over time. C. Plots the magnitude of the effect size of the between group differences in response variability over time. The effect sizes increase in a linear fashion. D. Drift rate. This is another means of quantifying loss of WM precision over time.

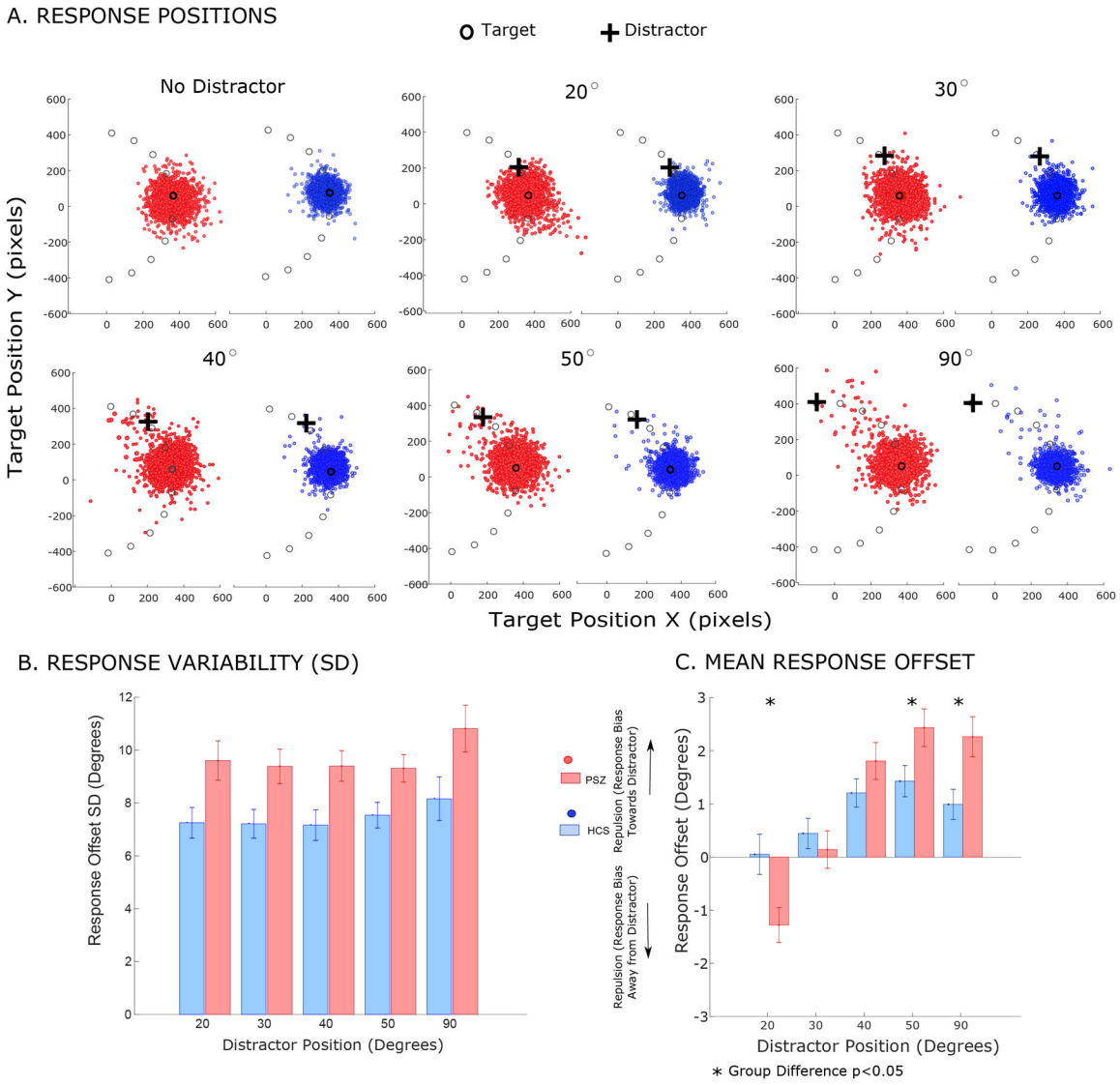

Figure 4. Impact of Distractors on WM precision.

A. Plots of individual responses with distractors presented at varying distances from the target. Note that at 20° there is a cluster of responses in the direction opposite of the distractor in PSZ but not HCS, whereas PSZ show a greater number of responses close to the distractor location at greater distractor distances. B. PSZ demonstrate less precise WM across distractor position. C. Mean Response Offset. PSZ show repulsion away from the nearest distractor position (values below 0 indicate repulsion; values above 0 indicate attraction in the direction of the distractor) but show attraction towards the most distant distractors..

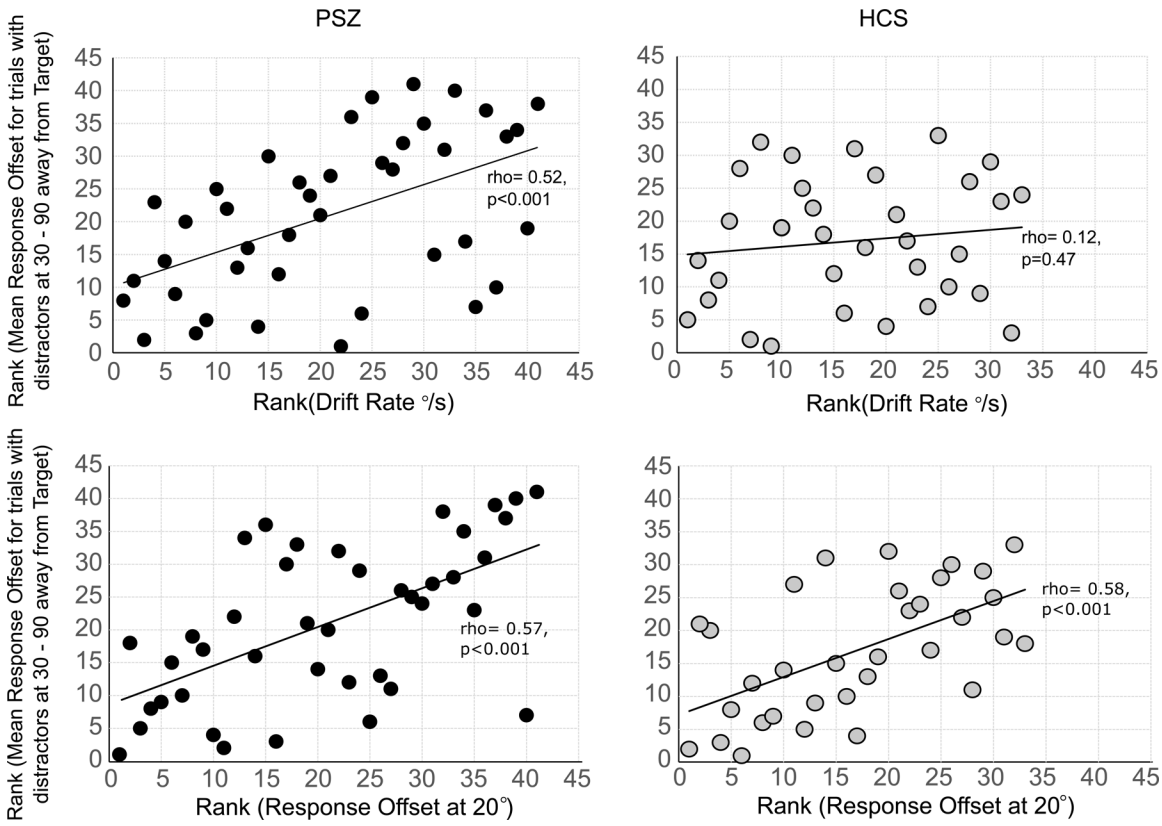

Figure 5. Association between drift rate and distractibility.

A. In PSZ, the loss of precision over increasing delay intervals was correlated with the extent to which their responses were biased towards the location of distractors. B. This effect was minimal in HCS.

Table 1:

Participant Characteristics

	NCS (N=33)	PSZ (N=41)	Statistic	*p* value
Age	31.13 (9.06)	36.17 (9.35)	*t = 1.86*	*0.07*
Gender (M | F)	19 | 13	24 | 17	*φ =0.01*	*0.94*
Race (African American | Caucasian | Other)	12 |18 | 2	15|21 | 5	*φ =0.75*	*0.67*
Participant Education	15.63 (1.68)	13.34 (2.36)	*t = 4.63*	*<0.001*
Maternal Education	15.47 (2.95)	14.39 (3.01)	*t = −0.90*	*0.37*
Paternal Education	14.58 (3.59)	13.87 (3.02)	*t =0.84*	*0.40*
WTAR (Wechsler Test of Adult Reading)	115.52 (10.30)	103.47 (15.75)	*t=3.74*	*<0.001*
Antipsychotic Medication				
Total CPZ		525.95 (379.45)		
Clinical Ratings				
BPRS Positive		2.09 (1.17)		
BPRS Negative		1.57 (0.46)		
BPRS Disorganization		1.22 (0.38)		
BPRS Total		31.58 (9.30)		
SANS AA		19.63 (9.64)		
SANS EE		11.43 (7.90)		
SANS Total		23.97 (11.43)		

Table 2:

Statistics

Delay Task	Test Value	P value	Effect Size[b]
Standard Deviation (Response Variability) (Fig 2A)			
Delay Duration[a]	F = 133.48	< .001**	η^2_p = 0.650
Group	F = 12.67	< .001**	η^2_p = 0.150
Delay Duration × Group[a]	F = 7.33	< .001**	η^2_p = 0.092
Drift Rate (°/s) (Fig 2C)			
t-test for group difference in WM drift	t = 3.39	< .001**	d = 0.794
Distractor Task			
Standard Deviation (Response Variability) (Fig 3B)			
Distractor Position[a]	F = 2.37	0.059	η^2_p = 0.032
Group	F = 8.75	0.004*	η^2_p = 0.108
Distractor Position × Group[a]	F = 0.46	0.749	η^2_p = 0.006
Response Offset (°)(Fig 3C)			
Distractor Position (excluding No distractor trials)	F = 43.25	< .001**	η^2_p = 0.375
Group	F = 0.43	0.512	η^2_p = 0.006
Distractor Position × Group	F = 10.65	< .001**	η^2_p = 0.129
Group differences for each Distractor Position (Response Offset)			
0 (No Distractor)	t_{72} = 1.265	0.210	d = 0.296 (−0.166, 0.756)
20	t_{72} = 2.660	0.010*	d = 0.622 (0.151, 1.089)
30	t_{72} = 0.649	0.518	d = 0.152 (−0.308, 0.610)
40	t_{72} = −1.325	0.189	d = −0.310 (−0.770, 0.152)
50	t_{72} = −2.113	0.038*	d = −0.494 (−0.958, −0.027)
90	t_{72} = −2.594	0.011*	d = −0.607 (−1.074, −0.136)

[a]Mauchly's test of sphericity indicates that assumption of sphericity is violated($p<0.05$), thus p-values are Greenhouse-Geisser corrected.

[b]effect sizes are η^2_p or Cohen's d. For t tests indicating group differences, lower and upper 95% CI are included in parentheses.

Table 3:

Spearman Correlations

		Overall Response Offset for distractors between 30°−90° away from Target	Response Offset for distractor at 20°	Drift Rate (°/s)	BPRS Positive Symptoms	Log-Transformed CPZ
Overall Response Offset for distractors between 30°−90° away from Target	rho	-	**0.58**	0.13	n/a	n/a
	p-value		**< .001*** **	0.47	n/a	n/a
Response Offset for distractor at 20°	rho	**0.58**	-	0.12	n/a	n/a
	p-value	**< .001*** **		0.50	n/a	n/a
Drift Rate (°/s)	rho	**0.52**	0.20	-	n/a	n/a
	p-value	**< .001*** **	0.21		n/a	n/a
BPRS Positive Symptoms	rho	0.29	0.23	0.28	-	n/a
	p-value	0.07	0.16	0.08		n/a
Log-Transformed CPZ	rho	**0.39**	**0.37**	**0.44**	**0.51**	-
	p-value	**0.01***	**0.022***	**0.005****	**< .001*** **	

Top right= HCS Correlations (Shaded); Bottom left, PSZ Correlations

BPRS=Brief Psychiatric Rating Scale; CPZ = Chlorpromazine equivalent