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Increased repulsion of working memory representations in schizophrenia

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Abstract

Computational neuroscience models propose that working memory(WM) involves recurrent excitatory feedback loops that maintain firing over time, along with lateral inhibition that prevents the spreading of activity to other feature values. In behavioral paradigms, this lateral inhibition appears to cause a repulsion of WM representations away from each other and from other strong sources of input. Recent computational models of schizophrenia have proposed that reduction in the strength of inhibition relative to strength of excitation may underlie impaired cognition, and this leads to the prediction that repulsion effects should be reduced in people with schizophrenia spectrum disorders (PSZ) relative to healthy control subjects (HCS). We tested this hypothesis in two experiments measuring WM repulsion effects.

In Experiment 1, 45 PSZ and 32 HCS remembered the location of a single object relative to a centrally-presented visual landmark and reported this location after a short delay. The reported location was repelled away from the landmark in both groups, but this repulsion effect was increased rather than decreased in PSZ relative to HCS. In Experiment 2, 41 PSZ and 34 HCS remembered two sequentially presented orientations and reported each orientation after a short delay. The reported orientations were biased away from each other in both groups, and this repulsion effect was again more pronounced in PSZ than in HCS.

Contrary to the widespread hypothesis of reduced inhibition in schizophrenia, we provide robust evidence from two experiments showing that the behavioral performance of PSZ exhibited an exaggeration rather than a reduction of competitive inhibition.

General Scientific Summaries

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DISCLOSURES

None of the authors has biomedical financial interests or potential conflicts of interest.

Although spatial working memory impairments are among the hallmark neurocognitive deficits in people with schizophrenia (PSZ), the neural mechanisms are not well-established. Formation of precise memory representations depends on the balance of excitatory and inhibitory processes, and this balance is thought to be disrupted in schizophrenia. Here we show that interactions between working memory representations are exaggerated in people with schizophrenia (PSZ), such that objects are remembered as being more dissimilar than they actually are, and counter to computational models emphasizing reduced inhibition in schizophrenia, these repulsion effects in PSZ are consistent with exaggerated competitive inhibition between similar representations of objects.

Keywords

lateral inhibition; recurrent excitation; cognition; cognitive impairment; schizophrenia; working memory

INTRODUCTION

Schizophrenia is a devastating neuropsychiatric disorder that typically leads to psychological distress, reduced educational and economic attainment, disrupted interpersonal relationships, and impaired physical health (Bowie et al., 2006; Fett et al., 2011; Green, 1996,2016). Although positive symptoms such as hallucinations and delusions are the hallmarks of schizophrenia, basic cognitive abilities are also impaired in people with schizophrenia spectrum disorders (PSZ) (Heinrichs & Zakzanis, 1998).

Cognitive impairment in PSZ is broader than what is typically observed following a focal lesion, suggesting that it may be a result of local circuit abnormalities that are distributed widely across the brain. In particular, substantial evidence suggests that the balance of excitation and inhibition *(E/I balance)* is altered in PSZ. The overall pattern is complicated because of homeostatic and compensatory mechanisms (Krystal et al., 2017) and the long-term impact of antipsychotic medications, but chronic PSZ are typically thought to exhibit a relative reduction in inhibition compared to healthy control subjects (HCS) (Dienel & Lewis, 2018). Such changes in E/I balance would be expected to impact multiple cognitive domains, including perception (Silverstein, 2016) and working memory (WM) (Murray et al., 2012).

E/I balance plays an important role in *attractor* models of WM (Johnson, Spencer & Schoner,2009; Wei, Wang & Wang, 2012). In these models, neurons that code similar feature values (e.g., similar locations) are linked via recurrent excitatory connections, which are essential for producing sustained activity once the evoking stimulus has terminated. As shown in Figure 1A, this produces a persistent *bump* of activation in the subset neurons that represent the stimulus. Neurons coding a given feature value also send lateral inhibitory signals to other neurons, which prevents the recurrent excitation from spreading broadly or drifting over time. The inhibition also plays an important role when two feature values must be maintained at the same time: in the absence of mutual inhibition, the activity corresponding to the two feature values could merge together into a single representation of an intermediate feature value. These models require a precise balance of excitation and

inhibition to allow the neural representation to persist over time (excitation) without drifting or merging (inhibition) (Lim & Goldman, 2013,2014).

In some attractor models (Johnson, Spencer & Schöner,2009; Durstewitz, Seamans & Sejnowski, 2000), both the recurrent excitation and the lateral inhibition are tuned to the feature being maintained in memory, but with a wider tuning curve for the inhibition. Evidence for tuned inhibition has been observed in macaque prefrontal cortex (Constantinidis & Wang, 2004). The tuned inhibition produces a *zone of suppression* around the activated feature value, further sharpening the representation (Figure 1A). Tuned inhibition has an important side effect: when two objects with similar feature values are simultaneously stored in WM, the lateral inhibition causes the peaks of activity for the two features to shift away from each other.

This *repulsion effect* is illustrated in Figure 1B, which shows the pattern of activity across a hypothetical population of neurons coding different feature values (e.g., different locations). When a single object is presented with a given feature value, the bump of activity is centered at that feature value, and the surrounding zone of inhibition sharpens and stabilizes this bump. However, when two objects are presented simultaneously (as in the bottom portion of Figure 1B), the lateral inhibition causes a “repulsion” effect in which the bumps of activation are shifted away from each other (see, e.g., the slight shift of the red arrows in the bottom portion of Figure 1B relative to the true feature values). This repulsion effect appears to have a behavioral analog, in which objects are remembered as being farther apart (in the relevant feature space) than they actually are (Kiyonaga & Egner, 2016; Bae & Luck, 2017). Although it is not possible to demonstrate that these behavioral repulsion effects are caused by lateral inhibition at the neural level, there is good correspondence between the behavioral repulsion effects and the qualitative predictions of computational models that employ lateral inhibition (Johnson et al., 2009).

Even larger repulsion effects can be observed when an individual is asked to remember a spatial location near a continuously visible landmark (as in the task shown in Figure 2). In this situation, the landmark presumably has a stronger and more precise representation than the memory representation. The zone of inhibition around the landmark therefore overpowers the relatively weak memory activation, causing the memory-related activation to shift away from the landmark. However, repulsion should be minimal when the spatial location of the to-be-remembered item is distant from the landmark and therefore falls outside of the zone of inhibition surrounding the landmark (Figure 1D). Behavioral studies of spatial working memory have confirmed these predictions, showing repulsion of memory representations away from nearby but not distant landmarks (Nelson & Chaiklin, 1980; Kerzel, 2002; Spencer & Hund, 2002; Schmidt, Werner & Diedrichsen, 2003;Bae & Luck, 2017).

The amount of repulsion should also depend on the strength of the lateral inhibition. Figure 1E shows the predicted effect of decreasing the inhibition by 50% relative to the level illustrated in Figure 1C. Some repulsion is still present in Figure 1E, but the memory peak is closer to the true value than in Figure 1C. It should therefore be possible to use memory repulsion as a behavioral metric of altered E/I balance in PSZ. Specifically, if inhibition is

relatively weak in PSZ relative to HCS, then PSZ should exhibit less repulsion between a landmark and a WM representation relative to HCS. Similarly, PSZ should exhibit reduced repulsion between two simultaneous WM representations relative to HCS.

The present study was designed to test these predictions. Experiment 1 examined repulsion of a spatial WM representation away from a visible landmark. Experiment 2 examined the repulsion between two orientation representations that were concurrently stored in WM. Contrary to expectations, we found that, in both experiments, repulsion was actually *greater* in PSZ than in HCS, which is the opposite of what would be expected from reduced inhibition in PSZ. Of course, behavioral data cannot provide a direct measure of cortical inhibition. Nonetheless, given that decreased rather than increased repulsion would be expected in PSZ given existing computational models, these findings represent a significant puzzle. For the computational models of WM to be valuable, they must be able to map neural circuit dysfunction onto quantifiable changes in behavior. The field of psychiatry needs more behavioral studies to tease apart puzzling findings such as ours, as well as to test how neuroanatomical evidence relates to cognitive function and behavior.

EXPERIMENT 1

In Experiment 1, participants were asked to remember the location of an object in the presence of a continuously visible landmark (Figure 2A). Repulsion should shift the memory away from the landmark, especially for stimuli presented close to the landmark. For sufficiently distant locations, the memories may become biased toward the center of the display, but this appears to reflect a different mechanism (Kerzel, 2002).

Methods and materials

Participants—Forty-five clinically stable, medicated outpatients meeting the criteria of the Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV; First et al., 1997) for schizophrenia(thirty-two) or schizoaffective disorder(thirteen) and thirty-two matched HCS participated. All participants provided informed consent for a protocol approved by the University of Maryland School of Medicine Institutional Review Board (Protocol HP00054557).

Demographic and clinical information is summarized in Table 1. Diagnosis was established using a best estimate approach in which information from a Structured Clinical Interview for DSM-IV (SCID) was combined with a review of medical records at a consensus diagnosis meeting. All patients were receiving antipsychotic medication at time of testing. HCS were recruited via local community businesses and online advertisements. None of the HCS had a current Axis 1 or 2 diagnosis (as established by a SCID) or reported a family history of psychosis. In PSZ, symptom assessments included the Brief Psychiatric Rating Scale (BPRS, Overall & Gorham, 1962) and the Scale for the Assessment of Negative Symptoms (SANS, Andreasen, 1989). All participants received the MATRICS Consensus Cognitive Battery (Nuechterlein et al., 2008; Kern et al., 2008,).

Stimuli and procedure—Stimuli were displayed on a 19-inch CRT monitor (100 Hz, 1,024 X 768 pixels) with a gray background at a distance of 100 cm. An eye tracker

(Eyelink1000, SR Research Ltd., Mississauga, Ontario) was used to assess gaze stability during the fixation period. Manual responses were collected using a computer mouse. Figure 2A displays the sequence of events in a trial. A continuously visible white vertical line (3° long) appearing at the top half of the display (bottom edge 2° above the fixation point) served as a landmark.

Each trial began with a red fixation cross (1°) appearing at the center for 2000 ms. This was followed by a white target circle (0.5°) appearing at one of eight horizontal locations, evenly spaced on a log scale (in visual angle degrees: [0.07 0.15 0.3 0.6 1.19 2.38 4.77 9.53]), to the right or left of the fixation cross, resulting in 16 equiprobable positions. Targets were centered 1.5° above the fixation cross. The target was visible for 200 ms and was followed by a 3000-ms retention period during which only the landmark and fixation cross were present. A response cue (a white crosshair atop the fixation cross) then appeared, prompting participants to indicate the remembered location of the target by using the mouse to move the crosshair to the remembered target location. The response was finalized by clicking the mouse button. This was followed by a 1200-ms intertrial interval during which only the visual landmark was visible. Each participant completed 192 trials (24 at each target position, in random order).

Analysis—Our main outcome measure was the *response bias,* quantified as the horizontal displacement of the reported location away from the actual target location on each trial (in degrees of visual angle). The response bias was given a positive sign if the reported location was away from the landmark (repulsion), and it was given a negative sign if the reported error was toward the landmark (attraction). Figure 2B displays examples of these cases. The data were collapsed for mirror-image target locations, producing eight different distances (relative to the landmark). For each of these distances, we computed the mean response bias across trials. Single-trial values that were greater than two standard deviations away from the participant's mean were excluded from all analyses because these were likely to reflect lapses of attention. We also used eye tracking to ensure that central fixation was maintained, thus controlling for the possibility that eye movements were used as a means of maintaining target position. Despite these exclusion criteria, >92% of trials were retained (PSZ, 92.97±2.7%; HCS, 94.04±3.0%, t= 1.64, p=0.11).

The mean response bias values for the individual participants were analyzed in a 2-way ANOVA with factors of group (PSZ vs. HCS) and distance from landmark (8 levels, one for each distance), with the Greenhouse-Geisser epsilon correction for nonsphericity.

Results

Response Bias—Figure 2C displays mean response bias as a function of target location (horizontal distance from the visual landmark) for each group. Both groups exhibited repulsion (positive bias values) except at the most distant locations, indicating that memories of targets presented near the landmark were repelled away from the landmark. The repulsion was small for targets presented extremely close to the landmark (0.07–0.15° away) and was largest for targets presented 0.3–1.2° from the landmark. Targets located more than 4.5° from the landmark were remembered as being closer to the landmark (attraction, indicated

by negative response errors). This nonmonotonic pattern led to a significant main effect of distance ($F_{(2.17,162.79)} = 98.10$, $p < 0.001$, $\eta^2_p=0.57$). Responses were more biased away from the landmark in PSZ than in HCS, leading to a significant main effect of group ($F_{(1,75)} = 7.66$, $p = 0.007$, $\eta^2_p=0.09$). This greater bias away from the landmark in PSZ was particularly evident for targets that were more than 0.5° from the landmark, resulting in a significant group X distance interaction ($F_{(2.17,162.79)} = 3.09$, p =0.044, $\eta^2_p=0.04$). Follow-up *t* tests indicated that PSZ exhibited a significantly greater positive bias than HCS at 0.6° ($t(75)=2.67$, p=0.009, Cohen's d=0.62), 1.2°($t(75)=3.13$, p=0.002, Cohen's d=0.72), 2.4° ($t(75)=2.39$, p=0.02, Cohen's d=0.55), and 9.5°($t(75)=2.62$, p=0.01, Cohen's d=0.61).

Although the study was designed to examine horizontal repulsion, the fact that the landmark was above the fixation point made it possible to examine vertical biases as well. We observed greater repulsion (downward displacement) in PSZ than in HCS, especially for targets located close to the landmark. T tests indicated that PSZ exhibited a significantly greater positive bias than HCS at locations 0.07°–0.60° horizontally away from the landmark (p values between 005–0.023), whereas there were no group differences for targets 1.19°–9.53° away (all p values>0.37; see supplemental material S8).

Absolute Response Error—In order to allow a comparison with previous research, we also computed the *absolute response error,* which reflects the precision of the WM representation. Figure 2D displays mean absolute response error as a function of target location (horizontal distance from the visual landmark) for each group. The absolute error increased as a function of target location in both groups, as evidenced by a significant main effect of distance ($F_{(1.83,136.93)} = 165.17$,$p <0.001$, $\eta^2_p=0.69$). The absolute error was greater in PSZ than HCS, especially at greater distances from the offset. This led to a significant main effect of group ($F_{(1,75)} = 11.47$, $p = 0.001$, $\eta^2_p=0.13$), but the group X distance interaction did not reach statistical significance ($F_{(1.83,136.93)} = 3.10$, $p = 0.054$, $\eta^2_p=0.04$). However, when we compared the slopes (inlay, Figure 2D) of the regression lines representing the increase in response error as a function of distance (which was on a log scale), we found that the slope for PSZ was significantly greater than the slope of HCS according to Welch's *t*-test, $t(70.09) = 2.31$, $p =0.024$, Cohen's d=0.51).

Correlations with clinical symptoms and neurocognitive measures—We examined associations between our WM response bias measure and several relevant neuropsychological measures, namely the working memory and attention domains from the MATRICS battery in both groups, as well as total symptom scores and medication dosage in PSZ. Overall bias was calculated as the average bias across distance from landmark. The Spearman rho correlation coefficients and corresponding *p* values are provided in Table 3. We observed significant correlations between WM bias and the working memory cognitive domain from the MATRICS battery in both groups. We did not observe any significant correlations between overall bias and symptom measures (SANS and BPRS totals), and there were no significant associations with medication dose. Total MATRICS scores were not associated with overall bias in either group.

We also included our measure of WM precision (absolute response error) in the set of correlations (see Table 3). Precision was not associated with the overall bias measure in

either group. Interestingly, we observed a correlation in PSZ between precision and the attention- vigilance domain from the MATRICS battery (Spearman's rho= −0.36, p=0.02), as well as with the overall MATRICS score (Spearman's rho= −0.46, p=0.001). We did not observe any correlations between precision and the neurocognitive measures in HCS (all ps> 0.34).

Discussion

We observed a greater repulsion bias in PSZ than in HCS, especially when the target was 0.6 to 1.2° of visual angle from the target. This is the opposite of the pattern that would be expected if working memory impairments in schizophrenia are the result of reduced inhibition, and these results instead suggest an exaggeration of competitive inhibition.

Both groups exhibited relatively little repulsion when the target was extremely close to the landmark (within 0.15°), which may reflect the greater precision for targets near the landmark. Both groups also exhibited attraction rather than repulsion when the target was more than approximately 5° from the landmark (which appears to reflect a different mechanism; Kerzel, 2002).

EXPERIMENT 2

Experiment 2 was designed to replicate and extend the surprising findings of Experiment 1. This experiment used orientation rather than spatial position as the to-be-remembered feature and examined repulsion between two concurrent WM representations (Figure 3A).

Methods and materials

All methods were identical to those used in Experiment 1, except as noted.

Participants—Forty-one PSZ (11 met Diagnostic and Statistical Manual of Mental Disorders-IV criteria for schizoaffective disorder and 30 for schizophrenia) and 34 HCS participated. Most of these individuals also participated in Experiment 1 (38 PSZ and 29 HCS). Table 2 provides the demographic and clinical information.

Stimuli and procedure—A black fixation dot was continuously present in the center of the display except during the intertrial interval. Two target stimuli were presented on each trial (see Figure 3A). Each target was a teardrop shape (3° long, 1° maximum width) presented at the center of the display. The orientation of a given target was selected with equal likelihood from 12 equally spaced values (separated by 30°, starting at 15° from upright). The orientations of the two targets on a given trial were independently randomized. Thus, the orientation difference between the two targets could be ±30°, ±60°, ±90°, ±120°, ±150° (96 trials each), or 0° and 180°.(For the 0° and 180° orientation difference, half the amount of trials(48 each) were presented).

After a 500-ms fixation dot, the first target was presented (200 ms), followed by a blank interval (750 ms), the second target (200 ms), and another blank interval (1000 ms). A response ring then appeared along with the text "1st orientation" or "2nd orientation" displayed at the top of the screen, indicating which target to report first. Participants

reproduced the orientation of the specified target using a computer mouse. The mouse pointer started at the fixation point; once the cursor was visible, a teardrop shape appeared at an orientation that matched the current position of the mouse. The participant then adjusted the mouse position until the teardrop matched the remembered orientation of the target shape. The participant pressed the mouse button to finalize the response. After a 500-ms blank period, a second response ring appeared along with an instruction to report the other target. This second report was followed by a 500-ms intertrial interval. The order of report for the two targets was randomized. After 16 practice trials, each participant completed 6 blocks of 48 trials over two sessions.

Analysis—The analyses again focused on *response error,* the angular difference between the actual target orientation and the reported orientation on each trial. To determine whether the response to one target was attracted toward or repelled away from the other target, the sign of the response error for the target being reported at a given moment was designated relative to the orientation of the target that was not being reported at that moment. The response error was given a positive sign if the reported orientation was away from the orientation of the other target, and it was given a negative sign if the reported error was toward the orientation of the other target. For example, consider a trial in which Target 1 had an orientation of 90° and Target 2 had an orientation of 120°. If a participant reported an orientation of 87° for Target 1, this would be designated as a response error of +3° (since it was 3° away from the actual orientation of Target 1, in the direction away from Target 2). If the observer reported an orientation of 118° for Target 2, this would be signed as a response error of −2° (because it was 2° away from the true orientation of Target 2, in the direction toward Target 1). The data from trials with no (0°) or a 180° orientation difference were excluded from all analyses because attraction and repulsion are not defined for this difference.

To increase the robustness of the results, we collapsed the data across the two targets on each trial, increasing the number of data points for each orientation difference. The data were further collapsed across mirror-image orientation differences, producing five different orientation differences (±30°, ±60°, ±90°, ±120° and ±150°). For each of these orientation differences, we computed the circular mean of the response errors. Response errors > ±30° were excluded as outliers that likely reflected lapses of attention or swapping of the two orientations (Bays, Catalao & Husain, 2009). This exclusion criterion removed 14.3% of trials [(PSZ, 20.7 ± 2.7%; HCS, 6.9±1.4%, t= 5.34, p<.001). Although more trials were excluded in PSZ than in HCS, the pattern across orientations was similar in the two groups. Considering the widespread cognitive control deficits in schizophrenia, including the impaired ability to maintain attentional focus, it is not surprising that in this task PSZ were more prone to attentional lapses than HCS.

Results

Response Bias—Figure 3B displays mean response bias as a function of the orientation difference between the two targets, separated by group. In both groups, the reported orientations for the two targets were biased away from each other when the two orientations were less than 90° apart (repulsion, indicated by positive response errors). However, when

the orientations were more than 90° apart, the responses to the two targets tended to be biased toward each other (attraction, indicated by negative response errors). Whereas HCS exhibited clear repulsion only when the two targets were within 30° of each other, PSZ exhibited clear repulsion up to at least a 60° orientation difference. The finding of more positive error values (repulsion) for orientations closer together and negative error values (attraction) for orientations further apart in both groups led to a significant main effect of orientation difference, ($F_{(3.10,226.34)} = 30.02$, $p < 0.001$, $\eta^2_p = 0.29$). The finding of repulsion over a wider range in PSZ than in HCS led to a significant group X orientation difference interaction effect ($F_{(3.10,226.34)} = 4.04$, $p = 0.007$, $\eta^2_p = 0.05$). The main effect of group was not significant ($F_{(1,73)} = 2.48$, $p = 0.12$, $\eta^2_p = 0.03$). Follow-up t tests indicated that PSZ exhibited a significantly greater positive bias than HCS at 60° ($t(73) = 2.78$, p=0.007, Cohen's d=0.65) and at 150° ($t(73) = 2.43$, p=0.018, Cohen's d=0.56).

Because we observed group differences in Age, we conducted additional analyses using Age as a covariate. Details of statistics are presented in supplemental materials (Section S1). Even though age may have explained some between-groups variance in this task, the analyses of covariance yielded the same results, with a significant main effects of orientation difference and a significant group X distance interaction. Thus, even though PSZ were somewhat older on average than HCS, this small age difference is unlikely to be driving between-group difference in response bias.

To achieve a reasonable number of trials per condition, we made an a priori decision to collapse the data across the first and second stimuli that were presented on a given trial and the first and second reports. However, as an exploratory analysis, we subdivided the data into the first and second stimulus and the first and second report. As detailed in the Supplemental material, the data were entered into a four-way ANOVA with within-group factors of orientation difference (near or far), presentation order (Target 1 or Target 2), and response order (Report 1 and Report 2) and a between-group factor of diagnostic group (PSZ versus HCS). As in a previous study with neurotypical young adults (Bae & Luck, 2017), we found a larger repulsion effect for the second sample stimulus than for the first sample stimulus and for the second report than for the first report. However, these effects were similar for both groups, and the increased repulsion for PSZ at the 60° orientation difference that was observed in the main analysis (Figure 3B) was present for the first and second sample stimuli and for the first and second report (Supplementary Figure S5).

Absolute Response Error—Figure 3C displays mean absolute response error as a function of the difference between the two orientations for each group. As in Experiment 1, the absolute error was greater in PSZ than HCS, leading to a significant main effect of group ($F_{(1,73)} = 25.61$, $p < 0.001$, $\eta^2_p = 0.26$). In both groups, the absolute error was also lower at the 0 and 180° orientation differences than at the other differences, leading to a main effect of orientation difference ($F_{(1,73)} = 59.97$, $p < 0.001$, $\eta^2_p = 0.45$). The group X orientation difference interaction did not approach statistical significance ($F_{(1,73)} = 0.60$, $p = 0.73$, $\eta^2_p = 0.008$).

Correlations with clinical symptoms and neurocognitive measures—As in Experiment 1, we examined associations between the WM response bias measure and the

working memory and attention domains from the MATRICS battery in both groups, as well as total symptom scores and medication dosage in PSZ. Table 4 displays Spearman rho correlation coefficients and corresponding *p* values. As in Experiment 1, we observed significant correlations between the overall bias and the working memory cognitive domain from the MATRICS battery in both groups. We did not observe any significant correlations between overall bias and symptom measures (SANS and BPRS totals) in PSZ, and our experimental measures were not correlated with medication dose. In PSZ, but not HCS, response bias was associated with total MATRICS score.

As in Experiment 1, our measure of precision (absolute response error) was not significantly associated with the overall bias measure in either group, but in PSZ (but not HCS) precision was significantly correlated with the attention-vigilance domain from the MATRICS battery (Spearman's rho= −0.43, p=0.005) as well as with the overall MATRICS score (Spearman's rho= −0.54, p<0.001).

Discussion

As in Experiment 1, PSZ exhibited greater repulsion than did HCS. Above-chance repulsion was present only with a 30° orientation difference in HCS, but repulsion extended at least to 60° in PSZ. These results are the opposite of what would be expected on the basis of prior evidence for reduced inhibition in PSZ.

In Experiment 1, the landmark was visible when the WM target was presented, so the repulsion effects may have occurred during the perception of the target. In Experiment 2, however, the two orientations were separated by 1500 ms, ruling out the possibility of purely sensory repulsion effects.

GENERAL DISCUSSION

Anatomical studies of cortical microcircuitry provide overwhelming evidence that schizophrenia is associated with impairments in GABAergic inhibitory circuitry (Lewis et al., 1999; Wassef, Baker & Kochan, 2003). However, glutamatergic excitatory systems are also disrupted (Hoftman, Datta & Lewis, 2017), and the overall pattern is complicated by homeostatic and compensatory mechanisms that unfold over development (Krystal et al., 2017) and by the long-term consequences of antipsychotic medications. Nonetheless, the overall E/I balance appears to be shifted toward a relative reduction of inhibition in chronic PSZ (Dienel & Lewis, 2018). GABA-mediated inhibition plays a key role in gamma-band oscillations (Gonzalez- Burgos, Cho & Lewis, 2015), which in turn appear to be important in WM and other aspects of perception and cognition (Jensen, Kaiser & Lachaux, 2007; Lisman, 2010), so a disruption of GABA-mediated inhibition in PSZ could play a role in the broad pattern of cognitive dysfunction that is associated with schizophrenia.

However, linking postmortem anatomical findings with behavior is challenging. The present study attempted to provide such a link by comparing the performance of PSZ and HCS in two WM paradigms in which reduced lateral inhibition would be expected to produce reduced repulsion. However, we found increased rather than decreased repulsion in PSZ relative to HCS in both paradigms. Moreover, the degree of repulsion was correlated with an

independent measure of WM from the MATRICS battery in both experiments. Interestingly, PSZ also exhibited both less precise representations than HCS (as quantified by the absolute response error), consistent with prior research on spatial WM (e.g. Park & Holzman, 1992; Lee & Park, 2005; Badcock et al., 2008; Starc et al., 2017). However, the degree of repulsion was uncorrelated with the precision of the representations, suggesting that these two aspects of WM reflect different underlying mechanisms.

The experimental paradigms used in Experiments 1 and 2 provide perhaps the most straightforward possible behavioral assessment of lateral inhibition in WM. If WM representations of metric features such as location and orientation inhibit each other, this would be expected to produce a repulsion of the underlying neural representations (see Figure 1). Thus, the finding of exaggerated rather than reduced repulsion in PSZ is a significant puzzle. However, behavioral responses do not provide a direct measure of neural inhibition, and we cannot rule out the possibility that the observed repulsion reflects some other mechanism. Nonetheless, the present paradigms have substantial face validity for measuring inhibition, and we know of no theory that can explain greater repulsion in PSZ than in HCS in these tasks (whether or not the repulsion reflects inhibition).

It is important to note that the repulsion effects can be explained by inhibition only if the inhibition is tuned (i.e., that the inhibition is limited to feature values that are relatively close to the to-be-remembered value). Some computational neuroscience models of WM instead involve global inhibition (i.e., equal inhibition for all feature values, independent of which feature is being maintained in WM; Durstewitz et al., 2000), which would not be expected to produce repulsion. Consequently, the finding of greater repulsion in PSZ than in HCS is not inconsistent with these models. However, these models cannot explain the repulsion effects that were observed here and in many previous studies (Nelson & Chaiklin, 1980; Kerzel, 2002; Spencer & Hund, 2002; Schmidt, Werner & Diedrichsen, 2003;Bae & Luck, 2017), which indicates that they are, at a minimum, incomplete.

What, then, can explain the present findings of exaggerated repulsion in PSZ? One possibility is that the repulsion reflects a compensatory response that PSZ develop to deal with reduced inhibition. In the absence of this compensatory intervention, their WM representations might actually exhibit attraction rather than repulsion, which could be catastrophic for performance (e.g., because representations of different objects might merge). They may therefore learn (presumably unconsciously) to bias their WM representations away from each other.

Another possibility is that the exaggerated repulsion is related to the *hyperfocusing* that PSZ exhibit in a range of attention and WM paradigms (Sawaki et al., 2017; Luck et al., 2014;2019). In these paradigms, PSZ focus their processing resources more narrowly but more intensely than do HCS. For example, both ERP and fMRI signals associated with WM maintenance are actually greater in PSZ than in HCS when a single object is being maintained in visual WM (Leonard et al., 2012; Hahn et al., 2018). If this hyperfocusing produces a stronger excitatory input to the neurons that represent an object in WM, the lateral inhibition produced by these neurons would increase, and this could potentially lead to greater repulsion. However, there is not yet a computational model of hyperfocusing, so

this potential explanation of the present results cannot yet be rigorously tested. In addition, the hyperfocusing account cannot readily explain why PSZ showed more repulsion (or less attraction) than HCS even at the largest differences between the feature values.

Alternatively, the well-documented neuroanatomical changes in PSZ may not produce changes in the performance of WM tasks, and the link between inhibition and symptoms may be more complex. Further, as is the case with most clinical studies, we cannot definitively rule out the effects of anti-psychotic medication or polypharmacy that may alter the E-I balance, thus affecting the experimental manifestation of behavior.

Conclusions

The present study provides the most direct test to date of the hypothesis that the disrupted E/I balance in schizophrenia has a specific impact on behavioral performance. There are other ways of explaining previous findings of decreased precision, increased rates of information loss, and greater distractibility in PSZ (Lee & Park, 2005; Fuller et al., 2005; Badcock et al., 2008; Anticevic et al., 2012; Erickson et al., 2014), but a reduction in repulsion would be specifically predicted by a reduction in lateral inhibition. Whereas reduced inhibition would be expected to produce less repulsion between representations, we found that repulsion was greater in PSZ than in HCS in two different experimental paradigms. Although we cannot be certain that the repulsion effects reflect neural inhibition, these results provide an important new phenomenon that must be explained by computational models of schizophrenia. Considering that cortical inhibition may mediate several cognitive operations including attention and memory, it ought to affect behavior, and more experimental studies are needed to establish the connection between neural circuitry and behavior. Indeed, we have recently obtained evidence for repulsion in a third paradigm (Gold et al., 2020). In this additional paradigm, repulsion was produced by distractors presented during the delay period of a working memory task, and PSZ exhibited greater repulsion than HCS. Even though present results provide a puzzle rather than a solution, this puzzle may inspire new research that ultimately leads to new insights into the microcircuitry of schizophrenia, and consequently important steps in development of new treatments.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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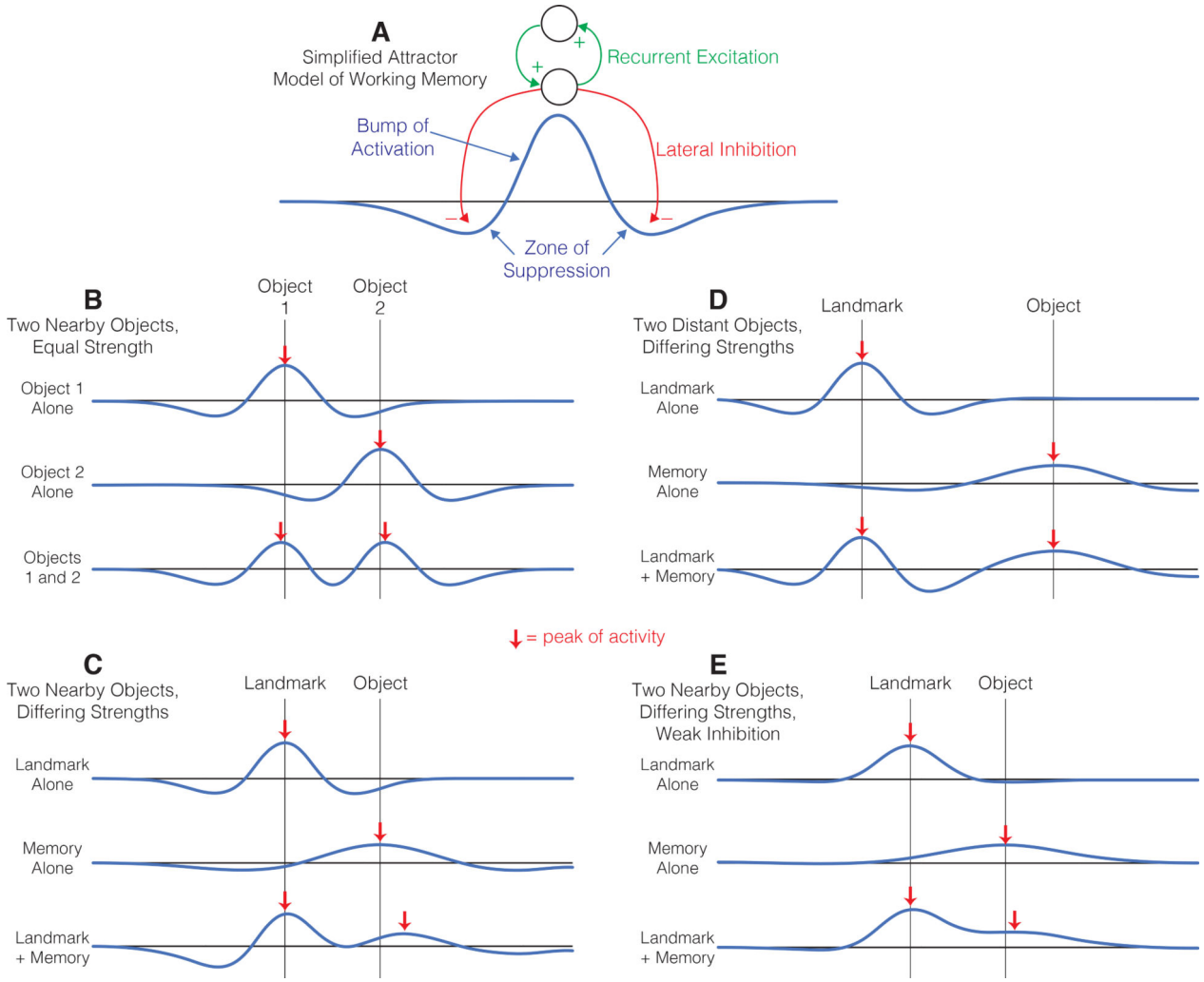

Figure 1.

Predictions of bump attractor models with tuned inhibition. (A) Basic model. Neurons (circles) that are selective for similar feature values (e.g., similar locations) are connected via recurrent excitation (green lines), and they also inhibit neurons that code adjacent feature values (red lines). This leads to a pattern of activity (blue line) with a positive peak (bump) near the true feature value and inhibition at surrounding values. Note that the X axis represents the space of feature values (e.g., locations) and the height of the curve represents the activity level of neurons coding that feature value. (B) Pattern of activity for two objects with similar feature values presented individually (top two curves) and presented simultaneously (bottom curve). The black vertical lines represent the true feature values. Note that the peaks of activity are shifted slightly outward from the true values when the two features are presented simultaneously. (C) Pattern of activity for a visible landmark and a weaker working memory representation. The peak for the working memory activity is repelled quite far from the true value. (D) Same as (C), but for objects with very different feature values. The peak of activity is now very close to the true value. (E) Same as (C), but with weaker inhibition. Note that the peak of activation exhibits less repulsion than in (C).

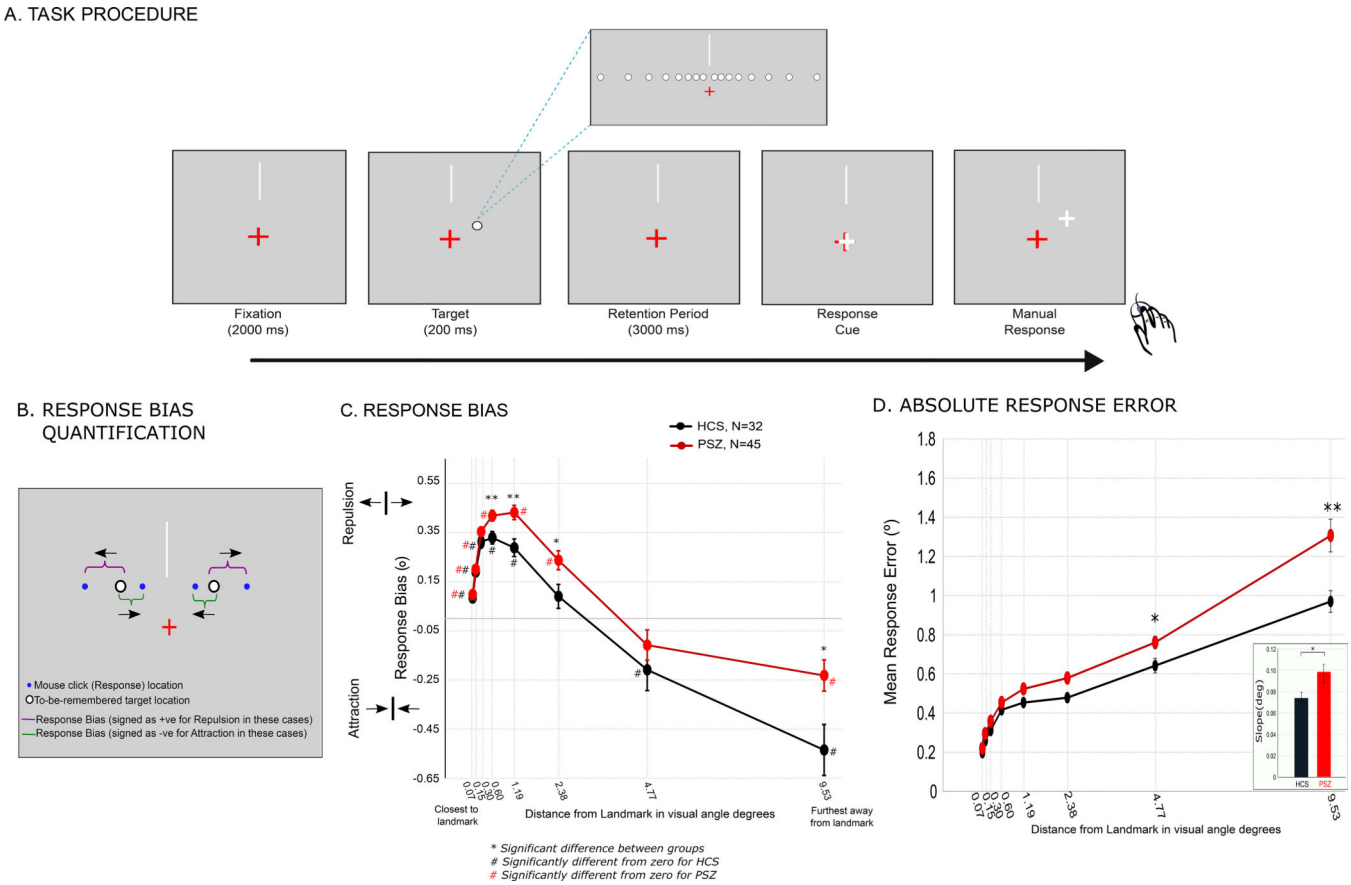

Figure 2.

Landmark Task. (A) Example of a trial in Experiment 1. A visual landmark, a white vertical line appearing at the top half of the display was continuously visible. Each trial began with a red fixation cross appearing at the center, followed by a white target circle appearing at one of 16 horizontal locations (displayed in the callout box), evenly spaced on a log scale, either to the right or the left of the middle of the display. The target circle was visible for 200 ms, followed by a retention period of 3000 ms during which only the visual landmark and fixation cross were present. At the end of this period, a response cue in the form of a white crosshair atop the fixation cross appeared, prompting participants to indicate the remembered location of the target circle by using the mouse to move the crosshair until it matched the remembered target location and clicking to finalize the response. (B)Response Bias Quantification. Response Bias was quantified as the horizontal displacement of the reported location away from the actual target location on each trial (in degrees of visual angle) and was given a positive sign if the reported location was away from the landmark (repulsion), and it was given a negative sign if the reported error was toward the landmark (attraction). The data were collapsed for mirror-image target locations, producing eight different distances (relative to the landmark). (C)Response Bias results. Mean response bias as a function of target location (horizontal distance from the visual landmark), separated by group. Asterisks indicate significant difference between the groups and hashtags indicate distances at which the bias as significantly different from zero in each group respectively. (black for HCS, red for PSZ) (D) Absolute Response Error. Mean unsigned error was

derived as a precision measure, as quantified as the absolute horizontal displacement of the reported location from the actual target location on each trial (in degrees of visual angle). Mean response error is displayed as a function of target location (horizontal distance from the visual landmark), separated by group (Red, PSZ, Black, HCS). In the inlay, the bars indicate the mean slopes of the regression lines between response error and distance(which was on a log scale) for each group.

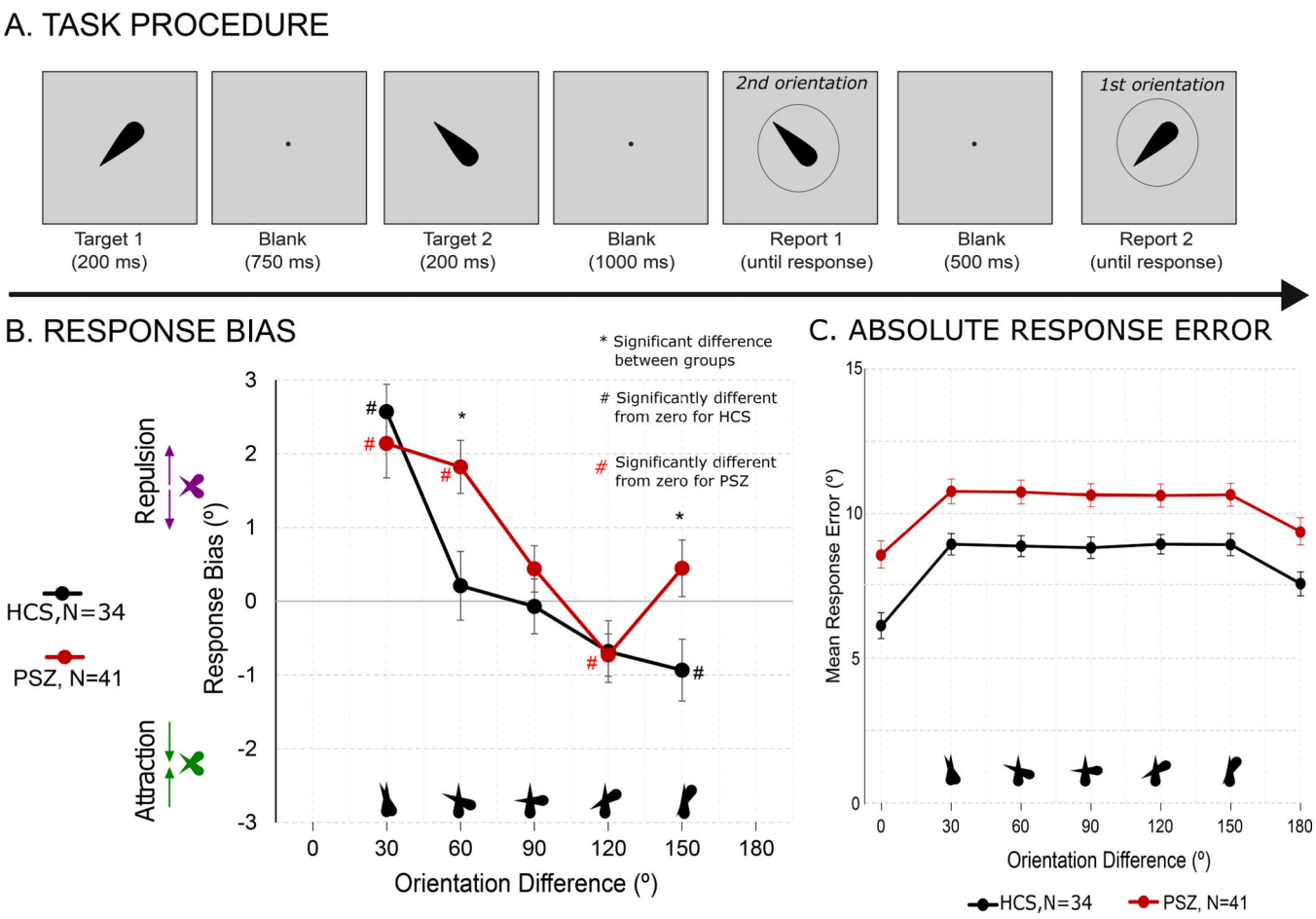

Figure 3.

Relative Orientation Task. (A) Example of a single trial. Participants remembered two serially presented target orientations and reproduced each orientation in a cued order. The cues ("1st orientation" and "2nd orientation") indicate that second target should be reported first in this example, but the order of report varied unpredictably across trials. (B) Mean response bias as a function of the orientation difference between the two items, collapsed across order of presentation and response order. The variable of interest is the angular deviation between reported orientation and actual orientation of the target being reported. To determine whether the response to one target was attracted toward or repelled away from the other target, the sign of the response error for the target being reported at a given moment was designated relative to the orientation of the target that was not being reported at that moment. The response error was given a positive sign if the reported orientation was away from the orientation of the other target, and it was given a negative sign if the reported error was toward the orientation of the other target. Positive error indicates bias away from the other target, and negative error represents bias toward the other target; the zero line indicates no bias. Asterisks indicate significant difference between the groups and hashtags indicate that the mean is significantly different from zero (black for HCS, red for PSZ). (C) Absolute Response Error. Mean absolute response error, quantified as the absolute value of the angular difference between the reported orientation and the actual target orientation on each

trial, is displayed as a function of the difference between the two orientations for each group. Absolute error was greater in PSZ (red) than HCS (black). In both groups, the absolute error was also lower at the 0 and 180° orientation differences.

Table 1:

Experiment 1 Participant Characteristics

	HCS (N=34)	PSZ[a] (N=45)	Statistic	*p* value
Age	32.22 (9.24)	35.78 (9.10)	*t= 1.68*	*0.10*
Gender (M | F)	20 | 14	29 | 17	*φ =0.15*	*0.70*
Race (African American | Caucasian | Other| Missing)	12 | 21 | 1| 0	17 | 23 | 5| 1	*φ =2.13*	*0.34*
Participant Education	15.67 (1.65)	13.24 (2.37)	*t= 5.10*	*<0.001*
Maternal Education	15.56 (2.88)	14.39 (3.04)	*t= 1.70*	*0.09*
Paternal Education	14.61 (3.56)	13.95 (3.15)	*t =0.84*	*0.40*
Neurocognitive Test Results				
WRAT 4	112.35 (11.03)	93.28 (11.97)	*t=7.07*	*<0.001*
MD Processing Speed	53.26 (7.21)	40.35 (15.05)	*t=4.72*	*<0.001*
MD Attention Vigilance	53.73 (8.14)	41.54 (12.49)	*t=4.81*	*<0.001*
MD Working Memory	53.16(8.64)	4137 (10.24)	*t=5.55*	*<0.001*
MD Verbal Learning	50.22 (12.37)	38.43 (8.04)	*t=5.24*	*<0.001*
MD Visual Learning	45.22 (11.19)	37.15 (11.39)	*t=3.19*	*0.002*
MD Reasoning	49.96 (8.71)	47.11 (11.97)	*t=1.44*	*0.16*
MD Social Cognition	54.48 (8.69)	42.00 (12.25)	*t=4.96*	*<0.001*
MCT Overall	52.53 (7.47)	36.21 (12.12)	*t=6.85*	*<0.001*
Medication				
Antipsychotic Medication (Atypical | Typical)		36 | 9		
Antipsychotic Medication :Total CPZ equivalents (mg)		565.78 (458.58)		
Other Psychotropic Medication[b]				
Antidepressants + Benzodiazepines		6		
Mood stabilizers + Benzodiazepines		3		
Mood stabilizers + Antidepressants		7		
Benzodiazepines		3		
Antidepressants		7		
Clinical Ratings				
BPRS Total		31.98 (9.18)		
SANS Total		22.72 (11.68)		

[a] Out of 45 PSZ, 32 met DSM-IV criteria for schizophrenia, and 13 for schizoaffective disorder

[b] Out of 45 PSZ, 26 were also (in addition to antipsychotics) receiving other psychotropic medications as indicated

WRAT = Wide Range Achievement Test; MD = MCCB (MATRICS Consensus Cognitive Battery) Cognitive Domain; MCT = MCCB Composite Total; CPZ = Chlorpromazine equivalent; BPRS=Brief Psychiatric Rating Scale; SANS=Scale for the Assessment of Negative Symptoms

Table 2:

Experiment 2 Participant Characteristics

	HCS (N=34)	PSZ[a] (N=41)	Statistic	*p* value
Age	31.92 (8.74)	36.10 (9.12)	*t = 2.01*	*0.05*
Gender (M | F)	23 | 11	24 | 17	*φ =0.66*	*0.42*
Race (African American | Caucasian | Other)	11 | 22 | 1	17 | 20 | 4	*φ =2.54*	*0.28*
Participant Education	15.68 (1.63)	14.22 (2.48)	*t = 2.94*	*0.0043*
Maternal Education	15.53 (2.83)	14.41(3.18)	*t = 1.60*	*0.12*
Paternal Education	15.12 (2.89)	13.73 (3.42)	*t =1.87*	*0.06*
Neurocognitive Test Results				
WRAT 4	112.3(10.57)	94.54 (11.77)	*t=6.67*	*<0.001*
MD Processing Speed	52.72 (8.06)	41.02 (15.6)	*t=3.85*	*<0.001*
MD Attention Vigilance	51.9 (9.68)	42.83 (12.26)	*t=3.39*	*<0.001*
MD Working Memory	53.09 (8.91)	42.49 (10.48)	*t=4.58*	*<0.001*
MD Verbal Learning	50.03 (12.32)	39.24 (8.29)	*t=4.46*	*<0.001*
MD Visual Learning	44.94 (10.99)	38.05 (12.03)	*t=2.52*	*0.014*
MD Reasoning	50.19 (8.26)	47.41 (11.69)	*t=1.14*	*0.26*
MD Social Cognition	52.81 (10.28)	43.39 (12.68)	*t=5.22*	*<0.001*
MCT Overall	52.68 (7.39)	34.91 (13.08)	*t=6.67*	*<0.001*
Medication				
Antipsychotic Medication (Atypical | Typical)		32 | 9		
Antipsychotic Medication :Total CPZ equivalents (mg)		564.3 (486.7)		
Other Psychotropic Medication[b]				
Antidepressants + Benzodiazepines		6		
Mood stabilizers + Benzodiazepines		3		
Mood stabilizers + Antidepressants		7		
Benzodiazepines		3		
Antidepressants		7		
Clinical Ratings				
SANS Total		31.47 (9.17)		
SANS Total		23.24 (11.31)		

[a] Out of 41 PSZ, 30 met DSM-IV criteria for schizophrenia, and 11 for schizoaffective disorder

[b] Out of 41 PSZ, 26 were also (in addition to antipsychotics) receiving other psychotropic medications as indicated

WRAT = Wide Range Achievement Test; MD = MCCB (MATRICS Consensus Cognitive Battery) Cognitive Domain; MCT = MCCB Composite Total; CPZ = Chlorpromazine equivalent; BPRS=Brief Psychiatric Rating Scale; SANS=Scale for the Assessment of Negative Symptoms

Table 3

Landmark Task: Spearman Correlations

	Overall Bias (°)	Absolute Error (°)	MD Attention Vigilance	MD Working Memory	MCTOverall	SANS Total	BPRS Total	Total CPZ
Overall Bias (°)	—	−0.11 0.54	0.00 0.98	*−0.36** *0.04*	−0.25 0.17	n/a	n/a	n/a
Absolute Error (°)	0.11 0.47	—	0.02 0.91	0.12 0.52	0.17 0.34	n/a	n/a	n/a
MD Attention Vigilance	0.10 0.51	*−0.36** *0.02*	—	0.13 0.47	0.32 0.08	n/a	n/a	n/a
MD Working Memory	***−0.41***** ***0.005***	−0.11 0.48	0.00 0.99	—	***0.60****** ***< .001***	n/a	n/a	n/a
MCT Overall	0.16 0.28	***−0.46***** ***0.001***	***0.72***** ***< .001***	0.10 0.53	—	n/a	n/a	n/a
SANS Total	0.00 0.98	0.11 0.49	0.08 0.61	0.10 0.52	−0.13 0.41	—	n/a	n/a
BPRS Total	−0.20 0.20	−0.02 0.91	−0.02 0.92	−0.14 0.37	−0.06 0.68	0.17 0.27	—	n/a
Total CPZ	−0.01 0.93	0.08 0.60	−0.13 0.41	−0.02 0.92	−0.02 0.89	0.22 0.15	0.25 0.10	—

* p < .05

** p < .01

*** p < .001

Values below the diagonal (left) are correlations for PSZ (Shaded gray), whereas those above (right, unshaded) are correlations for HCS.

For each variable pair, the top row indicates Spearman's rho, and the bottom row indicates the uncorrected *p* value.

Italicized values indicate correlation pairs that are significant without correction; Values in boldface are correlations that remained significant after Bonferroni correction. MD = MCCB (MATRICS Consensus Cognitive Battery) Cognitive Domain; MCT = MCCB Composite Total; SANS=Scale for the Assessment of Negative Symptoms; BPRS=Brief Psychiatric Rating Scale; CPZ = Chlorpromazine equivalent

Table 4

Relative Orientation Task: Spearman Correlations

	Overall Bias (°)	Absolute Error (°)	MD Attention Vigilance	MD Working Memory	MCT Overall	SANS Total	BPRS Total	Total CPZ
Overall Response Bias (°)	—	0.15 0.40	0.13 0.48	*−0.36** *0.04*	−0.20 0.28	n/a	n/a	n/a
Absolute Error (°)	0.18 0.25	—	0.05 0.77	−0.24 0.19	−0.18 0.32	n/a	n/a	n/a
MD Attention Vigilance	−0.01 0.96	***−0.43***** ***0.005***	—	0.27 0.14	***0.53***** ***0.002***	n/a	n/a	n/a
MD Working Memory	***−0.43***** ***0.005***	−0.16 0.33	0.2 0.21	—	***0.77****** ***< .001***	n/a	n/a	n/a
MCT Overall	*−0.35** *0.03*	***−0.54****** ***<0.001***	***0.73****** ***< .001***	0.26 0.09	—	n/a	n/a	n/a
SANS Total	0.06 0.70	0.07 0.66	0.05 0.77	−0.21 0.19	−0.04 0.79	—	n/a	n/a
BPRS Total	0.01 0.96	0.11 0.51	−0.07 0.66	0.16 0.33	0.02 0.89	0.3 0.06	—	n/a
Total CPZ	−0.04 0.79	0.11 0.49	−0.18 0.25	0.02 0.91	−0.14 0.37	0.21 0.19	*0.41** *0.01*	—

* p < .05

** p < .01

*** p < .001

Values below the midline(left) are correlations for PSZ (Shaded gray), while those above(right, unshaded) are correlations for HCS.

For each variable pair, top row indicates Spearman's rho, bottom row indicates uncorrected p-value Italicized values indicate correlation pairs that are significant without correction; Values in **bold** are those correlations that remain significant after Bonferroni correction MD = MCCB (MATRICS Consensus Cognitive Battery) Cognitive Domain; MCT = MCCB Composite Total; SANS=Scale for the Assessment of Negative Symptoms; BPRS=Brief Psychiatric Rating Scale; CPZ = Chlorpromazine equivalent.