Toward the Neural Mechanisms of Reduced Working Memory Capacity in Schizophrenia

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People with schizophrenia (PSZ) demonstrate reliable reductions in working memory (WM) capacity (i.e., the number of objects that can be held in memory). The present study asked whether WM impairments in PSZ can be explained by the same neural mechanisms that underlie individual differences in WM capacity among healthy individuals. Specifically, we examined event-related potentials in PSZ and healthy matched controls during a change detection task that required the storage of multiple objects in WM. The amplitude of contralateral delay activity (CDA), which correlates with WM capacity in healthy individuals, was larger in controls than in PSZ for memory loads of 3 and 5 objects, but larger in PSZ than in controls for a memory load of 1. This same pattern was found in the subgroups of PSZ and controls with an equivalent WM capacity. Moreover, the increase in CDA amplitude was correlated with individual differences in capacity in controls, but not in PSZ. These results demonstrate that WM impairment in PSZ is not associated with the same patterns of neural activity that characterize low WM capacity in healthy individuals. We propose that WM impairment in PSZ instead reflects a specific impairment in the ability to distribute attention broadly.

Keywords: CDA, event-related potentials, visual short-term memory

Introduction

Working memory (Miller 1956; Cowan 2001) provides a temporary storage buffer that is used to facilitate temporally extended tasks in everyday behavior (Hayhoe and Ballard 2005). People with schizophrenia (PSZ) show workingmemory (WM) impairments across a range of paradigms (Park and Holzman 1992; Gold et al. 2003, 2010; Barch 2005). Although computational neuroscience models of the underlying deficit have been proposed (Durstewitz and Seamans 2008; Lisman et al. 2008; Rolls et al. 2008), there is insufficient evidence about the nature of the WM impairment in PSZ to adequately constrain these models. In contrast, much is known about the neural activity that underlies individual differences in WM among healthy people, and our goal was to determine whether these mechanisms can also explain the observed WM impairment in PSZ.

Recent research on WM has often used visual change detection tasks (e.g., Fig. 1*A*; Luck and Vogel 1997) to compute *K*, an estimate of how many objects an individual has stored in WM (Pashler 1988). In healthy young adults, *K* is strongly correlated with the effectiveness of attentional selection: People who cannot filter irrelevant information have reduced an effective storage capacity for task-relevant objects (Vogel et al. 2005). In these paradigms, reduced storage of task-relevant objects is in turn associated with a corresponding reduction in electrophysiological and hemodynamic responses in the posterior parietal cortex (Todd and Marois 2004; Vogel and Machizawa 2004; Robitaille et al. 2009; Mitchell and Cusack 2011).

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Much research on impaired WM in schizophrenia has focused on the involvement of frontal cortical networks (e.g., Goldman-Rakic 1994; Manoach 2003), with less work directly examining the active storage of WM content in the posterior cortex. In the current study, we measured the neural activity associated with the maintenance of information in WM to ask whether the neural processes that vary with WM capacity in healthy control subjects (HCS) are also associated with the reduction in WM capacity observed in PSZ. That is, are PSZ simply at a lower point along the continuum of WM capacity than HCS, showing the same patterns of brain activity as healthy individuals who have relatively low capacity? Or is WM capacity reduced in PSZ because of a distinctive neural pathology that differs from the factors that are responsible for variation in capacity among healthy individuals?

Because PSZ are thought to have attentional impairments (Nuechterlein and Dawson 1984) and disruptions of the underlying prefrontal and striatal circuitry (Pantelis et al. 1997), one might expect that the increased storage of task-irrelevant information may explain the reduced WM capacity estimates in PSZ, just as it does in healthy individuals. However, prior studies have demonstrated no impairment in the ability of PSZ to selectively encode task-relevant information when it is embedded among equally salient distractors (Gold et al. 2006; Hahn et al. 2010; Spencer et al. 2011). Recent work has instead found that schizophrenia is associated with a "failure" to attend broadly (Elahipanah et al. 2011; Hahn et al. 2012), suggesting that impaired WM capacity estimates in PSZ may reflect a tendency to hyperfocus on a subset of the relevant information rather than an inability to filter irrelevant information.

To examine the neural activity associated with the active storage of information in WM, we recorded event-related potentials (ERPs) and measured the contralateral delay activity (CDA), a sustained negative voltage at posterior electrodes during the maintenance of WM. To isolate this ERP activity from other overlapping components, CDA experiments use a lateralized memory task, in which participants are cued to remember the information on one side of the display and ignore the information on the other side. By examining the difference in voltage between the hemisphere contralateral to the to-be-remembered information and the ipsilateral hemisphere, it is possible to subtract away other brain activity. This is especially important when comparing PSZ and controls, who may differ in other late ERP components that are unrelated to WM. We have previously shown that PSZ are unimpaired at using cues to select the appropriate subset of information for storage in WM under similar or even more challenging conditions (Gold et al. 2006).



Figure 1. (*A*) A no-change trial with memory load 3 in a block in which circles are to be remembered (as indicated by the outline shape at fixation). (*B*) *K*-score at each memory load. Group means with error bars representing the standard error are presented and values for individual participants in each group are plotted alongside the group means. Oval indicates those control participants included in the matched-group analysis that contained all PSZ. Box indicates those individuals included in the matched-group analysis that eliminated extreme participants from both groups. (*C*) Grand-average ERP waveforms time-locked to encoding array onset for HCS and PSZ groups, averaged across memory load. CDA is the differential activity between the contralateral and ipsilateral waveforms (shown filled in gray).

A hallmark of the CDA is that its amplitude increases as the number of objects in the encoding array increases but reaches an asymptote at an individual's WM capacity (Vogel and Machizawa 2004; Anderson et al. 2011; Gao et al. 2011). If PSZ have the same pattern of neural activity as healthy individuals with a low WM capacity, the relationship between CDA and capacity should be equivalent across groups, with the CDA reaching asymptote with fewer objects in PSZ than in HCS. Moreover, this hypothesis predicts that the CDA pattern in PSZ should be equivalent to that observed in lowcapacity HCS who are matched for WM capacity with the PSZ. In contrast, the hypothesis that WM capacity is reduced in PSZ because of a different mechanism predicts that the CDA should be qualitatively different in PSZ and HCS, even in subgroups that are matched on behavioral measures of capacity.

Materials and Methods

Participants

Twenty-seven participants meeting the criteria for schizophrenia or schizoaffective disorder and 23 HCS completed the task. Three participants in the PSZ group and 2 in the HCS group were excluded due

Table 1

Demographic features of sample

| | HCS group | | PSZ group | | Statistical comparison |
|--|------------------------------|----------------------------|------------------------------|--------------------|---|
| | Mean | Standard deviation (SD) | Mean | SD | |
| Age Education (years) Parental education (years) ^a Male/female | 40.4 15.4 14.5 14:7 | 10.3 2.1 2.7 | 40.2 13.4 14.3 17:7 | 10.7 2.2 2.9 | t(43) = 0.07, P = 0.94 t(43) = 3.13, P < 0.01 t(41) = 0.21, P = 0.83 $\chi^{2}(1) = 0.09 P = 0.76$ |
| Race (AA:W:U) Handedness (R:L:A) | 8:13:0 18:2:1 | | 10:13:1 23:1:0 | | $\chi^{2}(2) = 0.53, P = 0.59$ $\chi^{2}(1) = 2.6, P = 0.11$ |

Note: AA = African American, W = white, 0 = other, R = right-handed, L = left-handed, A = ambidextrous (not included in χ^2 analysis).

^aTwo participants in the PSZ group were not able to report parental education levels.

to excessively noisy electroencephalogram (EEG) data leading to the rejection of >25% of trials after artifact correction (see details below), which exceeds our standard criterion for study inclusion. The final sample described below therefore consisted of 24 PSZ and 21 HCS.

Diagnosis was established using a best estimate approach, which combines material from past medical records, collateral informants (when available), and the results of the Structured Clinical Interview for DSM-IV-TR Axis I Disorders to make a diagnosis based on the standard operational criteria in the Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV). Final diagnosis was reached at a consensus conference involving clinical staff chaired by co-author J.M.G. 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 (6 were receiving typical antipsychotics, 18 atypical antipsychotics, with 1 participant on both typical and atypical antipsychotics, 10 were diagnosed as paranoid, 8 as undifferentiated, 2 as residual, 1 as catatonic, and 3 as having schizoaffective disorder.

Control participants were recruited by random-digit dialing of households in nearby zip codes, and they were screened using the complete Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I; First et al. 2002) and Axis II Personality Disorders (SCID_IV; Pfhol et al. 1995). Controls had no current diagnosis of any Axis I disorder, Axis II schizophrenia-spectrum disorder, and denied a lifetime history of psychosis as well as no family history of psychotic disorders in first-degree relatives.

The demographics of the participants are shown in Table 1. No significant differences were found between groups in age, race, gender, parental education, or handedness. There was a difference in the number of years of education completed, which is typical given that the disease onset is generally in early adulthood.

All participants (PSZ and HCS) were free of other medical or neurologic comorbidity that might interfere with test performance, including substance abuse or dependence within the last 12 months. All participants were between the ages of 21 and 58 years of age, and gave written informed consent before taking part in the study. The protocol was approved by the Institutional Review Board at the University of Maryland School of Medicine.

Task Overview

Participants performed a lateralized change detection task akin to that of Vogel and Machizawa (2004), while the EEG was recorded. Each trial consisted of an encoding array in which to-be-remembered shapes appeared on one side of the display and the same number of irrelevant shapes on the other. Participants were required to remember the colors of the objects on one side of the encoding array (either the rectangles or the circles depending on block; see Fig. 1*A*). They maintained these objects in WM over the delay period, and then determined whether or not one of the to-be-remembered objects changed color in the test array.

Stimuli

The stimuli were presented on a cathode ray tube monitor at a distance of 70 cm, with a medium gray background (5.7 cd/m^2) . Each object subtended 0.65° . One, 3, or 5 objects of the to-be-remembered shape were presented on each trial in a lateralized fashion, occurring either all to the left or the right of fixation. On the opposite side, the same number of objects was shown in the irrelevant shape. The objects were positioned within 2 invisible rectangular regions, each 4° wide and 7.3° tall, positioned with the inner boundary either 1.5° to the left or the right of fixation. Object locations were chosen randomly within the appropriate region, except that a minimum distance of 2° between object centers was required.

On each trial, the color of each object in the encoding display was randomly chosen from a set of 12 colors without replacement. These colors were red (Commission Internationate de l'Eclairage *x*, *y* coordinates = 0.615, 0.351), green (0.205, 0.649), blue (0.148, 0.063), yellow (0.444, 0.470), purple (0.333, 0.315), cyan (0.227, 0.312), pink (0.416, 0.322), gray (0.250, 0.405), black (0, 0), white (0.338, 0.310), orange (0.458, 0.474), and magenta (0.319, 0.183). On a no-change trial, the test array was identical to the encoding array. On a change trial, the color of one randomly selected object from the attended side was changed to one of the remaining colors not used in the test display. This new color was constrained to be 1 of the 4 colors that were maximally distant from the original color in the color space, which ensured that the color changes were always highly perceptually discriminable.

Procedure

The encoding array was presented for 200 ms and the to-be-remembered objects were defined by shape. One side of the screen contained circles and the other side contained rectangles, with the side allocation varying randomly between trials. Participants were instructed to remember the colors of the circles for half the blocks and to remember the colors of the rectangles for the other half. The encoding array was followed by an 800-ms delay period in which only the fixation was shown (see Fig. 1A). A test display was then shown, and the participant had a maximum of 2000 ms to make a forced-choice response indicating whether one of the to-be-remembered objects had changed color or whether the display was the same as the encoding display. This was followed by a 1000-ms intertrial interval that only contained the fixation marker. A color change was present in one of the to-be-remembered objects on 50% of trials (changes never occurred in the other objects). Participants responded by pressing a button on a handheld gamepad with the index finger to indicate "change" and with the middle finger to indicate "no change." We have previously shown that PSZ are unimpaired at the type of selection required in this task, even under more difficult conditions in which the squares and circles are spatially intermixed (Gold et al. 2006). To ensure that participants could easily remember the task rule, an outline of the to-be-remembered shape for the current block was shown at fixation throughout the block. Each array had 1, 3, or 5 task-relevant objects; the number of task-relevant objects will be subsequently referred to as the "memory load." The instructions emphasized accuracy rather than speed. Participants were instructed to maintain the fixation at the center of the screen during each trial.

There were 12 trial blocks, with the to-be-remembered shape alternating between blocks. Overall, there were 300 trials at each memory load (i.e., 1, 3, or 5 to-be-remembered objects). At the beginning of the session, participants completed a practice block that contained only memory load 1 trials. Once the task was understood, another practice block containing both memory loads 1 and 3 trials was run, followed by a final practice that included memory loads 1, 3, and 5 trials.

After every 2 task blocks, participants performed a short eye movement block in which they were instructed to make an eye movement to an object that appeared briefly at a peripheral location for 750 ms. The object randomly appeared at 1 of 8 locations, which consisted of the 4 corners of the invisible regions in which objects could appear during the memory task. In each of the 6 eye movement blocks, 16 trials were completed. The EEG data from these blocks were used to

EEG Recording and Data Processing

The EEG was recorded from Ag/AgCl electrodes in an elastic cap, using a subset of the International 10/20 system sites (O1, O2, Oz, P3, P4, Pz, P7, P8, T7, T8, TP7, TP8, CP3, CP4, CPz, C3, C4, Cz, F3, F4, and F2). Data were recorded online with a left-mastoid reference, and re-referenced offline to the average of the left and right mastoids. Eye activity was monitored with 3 external electrodes. Blinks were monitored with an electrode placed below the left eye (using F3 as the reference). Eye movements were monitored using the horizontal electrooculogram (HEOG), measured between electrodes placed 1 cm lateral to the external canthi. Signals were amplified, filtered, and digitized with a Neuroscan Synamps amplifier (gain = 5000, half-amplitude bandpass = 0.05–100 Hz with a 60-Hz notch filter, sampling rate = 500 Hz).

Signal processing and analysis were performed in Matlab using the EEGLAB toolbox (Delorme and Makeig 2004) and ERPLAB toolbox (http://www.erpinfo.org/erplab). Preprocessing included the removal of time intervals that contained large muscle artifacts or extreme offsets (identified by visual inspection) and the application of a Butterworth high-pass filter with a half-amplitude cutoff of 0.05 Hz (roll-off = 12 dB/octave). Data were downsampled to 250 Hz (an antialiasing filter was automatically applied by the downsampling routine). Independent component analysis (ICA) was then performed on the continuous data to identify and remove components associated with eye movements and eye blink activity (Jung et al. 2000). Following the removal of these ICA components, a Butterworth low-pass filter was applied (half-amplitude cutoff = 36 Hz, roll-off = 12 dB/octave).

The ICA-corrected EEG data were segmented into epochs that began 200 ms prior to the onset of the encoding display and ended at the onset of the test display. Baseline correction was performed by subtracting the mean of the 200-ms pre-stimulus period. Epochs were rejected if any electrode contained offsets >200 µV over the course of the epoch. At each scalp site and the bipolar vertical electrooculogram (VEOG) channel, a window of 200 ms was moved across the data (in 100-ms increments) and any epoch where the peak-to-peak offset exceeded 150 µV in any window was also rejected. Finally, a 100-ms step function was applied to the bipolar HEOG (Luck 2005), and epochs were rejected if they contained changes >25 µV, equivalent to saccades >1.5° (Lins et al. 1993). We also analyzed the data solely using artifact rejection, without any ICA correction, and the results were comparable to those presented here (but with reduced statistical power owing to the smaller number of trials in the averages).

Measures and Analyses

Our primary behavioral measure was *K*, an estimate of the number of objects held in WM (Pashler 1988; Cowan 2001). Pashler's formula was used because the design did not include a postcue (see Rouder et al. 2011). Specifically, $K = n \times (HR - FA)/(1 - FA)$, where *n* is the number of to-be-remembered objects, HR is the hit rate, and FA is the false alarm rate.

The CDA was measured as the difference between contralateral and ipsilateral waveforms during the delay period, averaged over the lateral posterior electrode sites (O1, O2, P3, P4, P7, P8, CP3, CP4, TP7, and TP8). Contralateral waveforms were computed by averaging the right electrode sites for trials on which to-be-remembered objects occurred on the left side with the left electrode sites for trials on which to-be-remembered objects occurred on the right side. Ipsilateral waveforms were computed by averaging the right electrode sites for trials on which to-be-remembered objects occurred on the right side with the left electrode sites for trials on which to-be-remembered objects occurred on the left side. Figure 1C depicts the contralateral and ipsilateral waveforms (averaged over memory load) for each group. We initially measured CDA amplitude as the mean amplitude in separate early (400-700 ms) and late (700-1000 ms) time windows, but the pattern of results did not differ between these windows, so a single 400-1000 ms window was used for the main analyses.

The P1 wave was measured to assess differences between groups in early sensory processing. P1 amplitude was measured in 2 complementary ways. First, we measured the mean voltage of the P1 by using a typical range of 70–130 ms. Secondly, to account for individual differences in P1 latency, we also measured the local peak amplitude (Luck 2005) between 75 and 200 ms. These measurements were taken from the occipital electrode sites (waveforms averaged over O1, O2, and Oz), collapsing over those trials where the to-be-encoded objects were on the left and right of the display.

Analysis of variance (ANOVA) was used for all statistical analyses. Greenhouse–Geisser-corrected *P*-values are presented when violations of sphericity occurred (Jennings and Wood 1976).

Results

Behavioral Performance

Figure 1B shows K scores as a function of memory load, with the values from individual participants plotted alongside the group means. Mean K was near ceiling in both groups at memory load 1, but was reduced in PSZ compared with HCS at memory loads 3 and 5. K was entered into a 2-way ANOVA, with memory load (1, 3, and 5) and group (PSZ and HCS) as factors. Confirming the higher overall K in HCS, there was a significant main effect of the group ($F_{1,43} = 5.8$, P = 0.02). There was also the expected increase in K as more objects were available to be encoded ($F_{2,86} = 95.9$, P < 0.001). Importantly, the interaction was significant ($F_{2.86} = 4.4$, P = 0.02), indicating that PSZ showed a specific impairment with larger memory loads. Planned comparisons showed a significantly lower *K* in PSZ than in HCS for memory loads 3 (t(43) = 2.6, P = 0.013) and 5 (t(43) = 2.19, P = 0.034), but not for memory load 1 (t(43) = 1.7, P = 0.09). These results replicate a previous study showing that K is substantially reduced in PSZ for arrays that are near or above capacity, but not for arrays of 1-2 objects (Gold et al. 2006). The presence of reduced K primarily at larger set sizes, but not at set size 1, suggests that the observed deficit in PSZ does not reflect nonspecific factors such as lapses of attention or poor perceptual abilities.

Contralateral Delay Activity

Grand-average ERP difference waves (contralateral minus ipsilateral) are shown in Figure 2A for both PSZ and HCS, illustrating the CDA at each memory load; mean CDA amplitudes are summarized in Figure 2B. In both groups, the difference waves diverged from 0 µV approximately 200 ms after the onset of the encoding array. The initial part of this effect (ca. 200-300 ms) presumably included activity associated with the N2pc component, which is lateralized like the CDA but reflects perceptual-level selection (Luck 2012). However, this early portion may have included CDA as well as N2pc, so the present design does not provide a pure measure of N2pc activity (which is normal in PSZ when attention is directed to a single visual search target; Luck et al. 2006). To avoid contaminating our CDA measure with N2pc activity, we began the CDA measurement period at 400 ms, by which time the N2pc has ordinarily terminated.

In both groups, the CDA was larger at memory loads 3 and 5 than at memory load 1. The CDA was substantially smaller for PSZ than for HCS at memory loads 3 and 5, which is consistent with the lower *K* observed for PSZ than for HCS at these memory loads. In contrast, the CDA was larger in PSZ than in HCS at memory load 1. Thus, PSZ do not simply exhibit decreased CDA amplitude but actually have a larger CDA than HCS under some conditions.

To assess the statistical significance of these results, we initially measured CDA amplitude in separate early (400–700 ms) and late (700–1000 ms) time windows and conducted a 3-way ANOVA with factors time window (early vs. late), memory load (1, 3, and 5) and group (PSZ and HCS). There was no main effect of time window ($F_{1,43} = 1.98$, P = 0.17). However, time did interact with memory load ($F_{2,86} = 4.34$, P = 0.02), reflecting a drop in CDA amplitude over time in both PSZ and HCS that were particularly pronounced at the higher memory loads. Importantly, there was no interaction of time window and group ($F_{1,43} = 0.03$, P = 0.96) and no time window × memory load × group interaction ($F_{2,86} = 1.15$, P = 0.32). The finding that CDA amplitude does not decline faster



Figure 2. (A) Grand-average ERP waveforms time-locked to encoding array onset showing the CDA difference waves (computed by subtracting the ipsilateral from the contralateral waveforms seen in Fig. 1*C*). (*B*) The mean amplitude of CDA between 400 and 1000 post-stimulus.

in PSZ than in HCS is consistent with recent empirical work by Gold et al. (2010) and a meta-analysis by Lee and Park (2005) that found no evidence of faster decay of WM representations in PSZ than in HCS.

The ANOVA yielded a significant main effect of memory load ($F_{2,86}$ = 34.7, P < 0.001), reflecting the increase in CDA with increasing memory load. The interaction of memory load and group was also significant ($F_{2,86}$ = 12.4, P < 0.001), reflecting the fact that the CDA was larger in HCS than in PSZ at memory loads 3 and 5 but larger in PSZ than in HCS at memory load 1. Given that there were no significant interactions of group with time window, the average over the full time window (400–1000 ms) is used in all subsequent analyses. CDA amplitude in this time window is summarized in Figure 2*B*, which confirms the patterns visible in the waveforms in Figure 2*A*.

Pairwise *t*-tests in this window confirmed a larger CDA for HCS than for PSZ at memory loads 3 (t(43) = 2.1, P = 0.046) and 5 (t(43) = 3.0, P = 0.004), along with the larger CDA for PSZ than for HCS at memory load 1 (t(43) = 2.06, P = 0.046). Moreover, 1-sample *t*-tests demonstrated that the CDA for memory load 1 was significantly >0 µV in PSZ (t(23) = 3.2, P = 0.009) but not in HCS (t(20) = 0.58, P = 0.57). Note that the CDA reflects the difference in activity between the hemisphere contralateral to the to-be-remembered side and the hemisphere contralateral to the to-be-ignored side, and it is therefore, in part, a measure of selective processing. The finding of a greater CDA in PSZ than in HCS at memory load 1 therefore suggests that PSZ were actually more selective than HCS in representing only the relevant object when the display contained a single object on each side.

Matched-Group Analysis

The finding of a larger CDA at memory load 1 in PSZ compared with HCS argues against the hypothesis that PSZ, like low-K healthy individuals, have a low K because of a deficit in preventing task-irrelevant information from reaching WM. However, to conclusively demonstrate that PSZ are not simply like low-K HCS, it is necessary to show that the pattern of neural activity in PSZ is different from that exhibited by HCS who have the same WM capacity. We therefore analyzed CDA amplitude in subsets of our PSZ and HCS samples that were matched for K scores at memory load 3. We used memory load 3 rather than memory load 5 because filtering deficits may produce declines in K for supracapacity arrays (Weiss et al. 1988; Gold et al. 2003; Vogel et al. 2005; McNab and Klingberg 2008). There are many different ways to create matched subgroups. We report the results from 2 complementary approaches, both of which equate the mean K values as well as possible while excluding as few participants as necessary to avoid jeopardizing the generality of the findings and reducing statistical power.

Our first approach involved comparing the entire group of PSZ to a subgroup of HCS that excluded the individuals with relatively high K values. This allowed us to ask very directly whether the reduced capacity in PSZ is accompanied by the same neural activity that characterizes HCS who have relatively low capacity. To accomplish this, we included all except the 7 HCS who had the highest K scores and who formed an obvious cluster at the top of the K distribution. The remaining subgroup of HCS (indicated by an oval in Fig. 1*B*) did not

differ significantly in K from the PSZ ($F_{1,36} = 0.32$, P = 0.58), nor was there a group by memory load interaction ($F_{2,72}$ = 0.58, P = 0.56). Despite having approximately the same behavioral performance (Fig. 3A), the groups did not exhibit the same CDA pattern. Just as in our comparison of the whole HCS group to the PSZ, we found that the CDA was elevated at memory load 1 and reduced at memory loads 3 and 5 in PSZ relative to the K-matched HCS subgroup (see Fig. 3B). In a group × memory load CDA analysis, the different CDA patterns led to a significant group × memory load interaction $(F_{2,72} = 5.45, P = 0.013)$, just as in the original whole-groups analysis. Moreover, the CDA was significantly elevated at memory load 1 for PSZ relative to the K-matched HCS subgroup (t(36) = 1.85, P = 0.05). The CDA at memory loads 3 and 5 was lower in this HCS subgroup than in the whole HCS group, as would be expected given that the CDA typically asymptotes at a lower level in healthy individuals with low capacity (Vogel and Machizawa 2004; see also the correlational analyses in the next section). T-tests comparing the CDA between PSZ and the K-matched HCS subgroup were no longer significant at memory loads 3 (t(36) = 0.97, P = 0.33) and 5(t(36) = 1.81, P = 0.12).

Our second approach to comparing K-matched subgroups was to eliminate individuals from both groups who had very high or very low K values, making it possible to ask whether the effects observed in our previous analyses remain when the most extreme individuals are excluded. Specifically, we eliminated 3 HCS whose K scores were above the range of the PSZ group, as well as the 2 HCS who performed well below everyone else in the HCS group. We also eliminated the 8 PSZ with the lowest K scores. This led to approximately equal mean K values for the 2 subgroups, with no significant effect of group ($F_{1,30} = 0.62$, P = 0.44) or group × memory load interaction ($F_{2,60} = 0.48$, P = 0.62). The rectangle in Figure 1B indicates the individuals who were included in this matched-group analysis (N=16 per subgroup). Despite the fact that behavioral performance was nearly equal in the matched subgroups (Fig. 3C), we found very different CDA patterns in these subgroups (see Fig. 3B). As before, CDA amplitude in these subgroups was greater in PSZ than in HCS at memory load 1, but smaller in PSZ than in HCS at memory loads 3 and 5, yielding a significant memory load x group interaction ($F_{2,60} = 11.7$, P < 0.001). The CDA at memory load 1 was again greater for PSZ than for HCS in these matched subgroups (t(30) = 2.2, P = 0.04). Conversely, the CDA was marginally significantly larger for HCS than for PSZ at memory load 3 (t(30) = 1.9, P = 0.056) and significantly larger at memory load 5 (t(30) = 2.4, P = 0.025). These results suggest that PSZ and HCS with intermediate WM capacity levels achieve these levels via different neural mechanisms.

These 2 methods represent 2 distinct ways of matching performance, but they converge on the same pattern of results. In both methods, the crucial group × memory load interaction was significant. Moreover, both methods yielded a significantly greater CDA amplitude at memory load 1 in the PSZ group compared with the matched HCS group. The only difference between these approaches was that, although the mean CDA amplitude at memory loads 3 and 5 was numerically lower in the PSZ group relative to the matched HCS group in both approaches, these differences reached a statistical significance only in the second approach. The most parsimonious explanation for this minor difference is that the



Figure 3. (A) K scores for groups containing all PSZ, with the best performing HCS eliminated. (B) The mean amplitude of CDA between 400 and 1000 post-stimulus for the group in (A). (C) K scores for groups matched by eliminating participants from both groups that had extreme K-scores at memory load 3. (D) The mean amplitude of CDA between 400 and 1000 post-stimulus for the groups shown in (C).



Figure 4. A scatter plot showing each participant's K score at memory load 3 against the increase in CDA amplitude between memory loads 1 and 3 for the HCS and PSZ groups.

reduction in sample size in the subgroup analyses led to a reduction in statistical power, increasing variability and making it more difficult to reach a statistical significance.

Correlations Between CDA and Behavior

To more specifically examine the relationship between the CDA and K, we examined correlations between measures (using the full sample of participants to avoid a restriction of range). In previous research with healthy young adults, CDA

increased with memory load up to an individual's capacity, which led to a strong correlation between capacity and the change in CDA between small and intermediate memory loads (Vogel and Machizawa 2004). Figure 4 shows this *K*–CDA relationship in PSZ and HCS. Specifically, we examined the correlation between the *K*-score at memory load 3 and the increase in CDA amplitude between memory loads 1 and 3. Consistent with previous research, this correlation was significant in HCS (Pearson's r=0.59, P=0.005) but not in PSZ



Figure 5. A scatter plot showing each participant's K score between memory loads 3 and 5 against the CDA amplitude at memory load 1.

(Pearson's r=0.03, P=0.987), and the difference in correlation between groups was statistically significant (z=2.0, P=0.045, 2-tailed). Due to the skewed distribution of Kvalues, we also calculated these correlations using Spearman's rank order correlation and found the same pattern (HCS: $r_s =$ 0.51, P=0.017; PSZ: $r_s=0.01$, P=0.96). Note that K was assessed at memory load 3 because K declined at memory load 5 in some participants, but the same pattern of results was obtained when we used K at memory load 5. Thus, PSZ did not show the typical relationship between K and CDA amplitude, providing further evidence for a qualitative rather than a quantitative difference in WM between PSZ and HCS.

We also examined correlations between K and the CDA at memory load 1 to see if hyperfocusing in PSZ (i.e., a large CDA at memory load 1) was associated with individual differences in memory performance. Because the analyses described above showed that the overselection effect was present in PSZ even when subgroups with equal K were compared, overselection does not seem like a likely explanation for the overall group difference in K at memory load 3. However, PSZ tend to exhibit a drop in K as the memory load increases beyond their storage capacity (Gold et al. 2003, 2006), and this may reflect an increasing tendency to overselect among the to-be-remembered objects when the WM system is challenged by higher loads. That is, the same tendency that leads to hyperfocusing on the attended side when each side contains only one object might lead to hyperfocusing on a subset of the information on the attended side when the display contains 5 items on each side. In this case, we would expect that K would drop between memory loads 3 and 5 in those PSZ who exhibit evidence of overselection (large CDA at memory load 1). To examine this, we correlated the amplitude of the CDA at memory load 1 with the change in K between memory loads 3 and 5 (Fig. 5). HCS showed no significant relationship between these 2 measures (Pearson's r = -0.211, P = 0.36). In contrast, PSZ exhibited a strong negative correlation (Pearson's r=0.649, P=0.001). That is, PSZ with a large CDA amplitude (i.e., a large negative value) at memory load 1 were also likely to exhibit reduced K at memory load 5 relative to memory load 3 (i.e., a negative

change in *K*). The difference in correlation between PSZ and HCS was marginally significant (z = 1.74, P = 0.08, 2-tailed), so we cannot conclude with confidence that this overselection pattern is present only in PSZ. However, the correlation within PSZ was quite high, accounting for 42% of the variance, so we can confidently conclude that the ERP evidence of overselection at memory load 1 in PSZ is strongly related to their behavioral performance at higher memory loads. (Spearman's rho was also significant for PSZ, $r_s = 0.67$, P < 0.001, but not for HCS, $r_s = 0.26$, P = 0.26.)

Hemispheric and Laterality Effects

Previous work has suggested that there may be atypical hemispheric asymmetry in PSZ, with impairments specific to the left prefrontal system (Posner et al. 1988; Park 1999). Because a lateralized frontal impairment might lead to deficits in posterior memory maintenance specific to one hemisphere, we ran an additional ANOVA that the contained electrode hemisphere (left and right) and attended side (contra and ipsi) as factors, in addition to the group (HCS and PSZ) and memory load (1,3, and 5). There was no main effect of hemisphere $(F_{1,43} = 0.09, P = 0.77)$, nor was there any significant interactions involving both the hemisphere and group (all P's >0.33). In addition, we conducted separate analyses of CDA amplitude for trials in which the attended items were in the left and right visual fields. For both visual fields, the interaction of group and memory load was significant (left: $F_{2,86}$ = 6.1, P < 0.01; right: $F_{2.86} = 4.6$, P = 0.02), providing further evidence that our CDA effect was not driven by a single hemisphere.

Because a relationship between left-handedness and schizophrenia has been reported (Green et al. 1989), we also conducted the main CDA analyses excluding the left-handed and ambidextrous participants from both groups. The significant interaction of memory load and group was again found ($F_{2,78} = 10.4$, P = 0.001), accompanied by a significantly larger CDA for memory load 1 in PSZ than in HCS (t(39) = 2.10, P = 0.04) and a significantly smaller CDA for memory load 5 in PSZ than in HCS (t(39) = 2.67, P = 0.01).

Early Sensory Activity: Correlations with P1 Amplitude

Recent studies have suggested that WM deficits in PSZ could stem from low-level sensory deficits (Haenschel et al. 2007; Dias et al. 2011), although other studies have demonstrated that reduced visual WM capacity can be observed in PSZ even when sensory precision is factored out (Gold et al. 2010). Despite this controversy, it is clear that the amplitude of the P1 sensory response is reduced in PSZ (Foxe et al. 2001; Schechter et al. 2005; Luck et al. 2006). This reduction in P1 amplitude was also observed in the present data, especially at the most posterior occipital electrode sites. Separate ANOVAs were conducted with the mean and peak P1 amplitude measures, using factors of memory load and group. The reduced P1 amplitude in PSZ led to a significant main effect of group for the peak amplitude measure ($F_{1,43} = 6.1$, P = 0.018) and a strong trend for the mean amplitude measure ($F_{1,43}$ = 3.6, P = 0.06). However, there was no main effect of memory load (peak: $F_{2,86} = 0.20$, P = 0.82; mean: $F_{2,86} = 2.5$, P = 0.11), nor an interaction of memory load and group (peak: $F_{2,86}$ = 0.02, P = 0.98; mean: $F_{2.86} = 0.57, P = 0.5).$

To determine whether this reduction in the sensory response might explain the WM impairments in PSZ, we examined correlations between P1 amplitude and multiple WM measures, separately for PSZ and HCS (see Table 2). None of these correlations approached significance except for a marginally significant correlation between P1 mean amplitude and CDA amplitude at memory load 3 in HCS (P= 0.056). Overall, there was no evidence that sensory processing deficits could explain either the reduced *K* or the CDA abnormalities in PSZ. Thus, although there was a significant evidence that this contributed to the WM impairments in our study.

Medication Analyses

It is always challenging to rule out the possibility that differences in neural activity between PSZ and HCS are a consequence of medications. However, it is possible to determine whether the considerable individual differences among PSZ could be explained by the different types of medications they are receiving. We examined CDA amplitude using ANOVAs with memory load and drug group as factors, comparing those who were taking typical (n = 5) versus atypical antipsychotics (n = 17), those taking selective sertonin reuptake inhibitors (n = 11) versus those not (n = 13), those taking a benzodiazepine (n = 15) versus those who were not (n = 9), and those taking antiparkinsonian drugs (n = 4) versus those

Table 2

P1 correlations with K and CDA

| | HCS group | | PSZ group | | |
|----------|----------------|----------------|----------------|----------------|--|
| | Mean amplitude | Peak amplitude | Mean amplitude | Peak amplitude | |
| K at 1 | -0.140 | -0.070 | -0.144 | -0.165 | |
| K at 3 | 0.248 | 0.070 | -0.184 | -0.214 | |
| K at 5 | 0.208 | 0.041 | -0.226 | -0.151 | |
| CDA at 1 | -0.399* | -0.135 | 0.043 | 0.363* | |
| CDA at 3 | -0.425** | -0.344 | 0.190 | 0.221 | |
| CDA at 5 | -0.315 | -0.225 | 0.237 | 0.324 | |

*0.073 < *P* < 0.10.

**P = 0.056.

not (n = 20). In none of these analyses did the main effect of drug group or the interaction between drug group and memory load approach significance. In addition, we computed chlorpromazine equivalents for each of the PSZ and examined the correlation between this measure and several CDA measures: CDA amplitude at each memory load, difference in CDA between memory loads 1 and 3, and difference in CDA between memory loads 3 and 5. None of these correlations approached significance

(P>0.31 in all cases). Thus, there was no evidence that medications influenced the present results, which accord with previous evidence indicating that WM deficits in PSZ are not a consequence of medication (Barch et al. 2001; Brahmbhatt et al. 2006).

Other Correlated Measures

Working memory is a complex construct that includes, in addition to storage capacity, the maintenance of information for several seconds in the face of distraction and the updating and manipulation of this information. Many different paradigms can be used to investigate WM, but we have chosen the change detection task because it provides a relatively pure measure of the storage capacity component. To ensure that our K measure is related to standard clinical measures of WM performance, we calculated the correlation between K and the Working Memory Domain score from the MATRICS battery (which is composed of a spatial span task and the letter-number sequencing test; Nuecherlein and Green 2006). These data were available for 19 of the 21 participants in the HCS group and for 23 of the 24 participants in the PSZ group. We found significant correlations between K and the MATRICS WM score in both HCS and PSZ (see Table 3). Similar correlations between K and the MATRICS battery were observed previously, using a related method for measuring K(Gold et al. 2010).

Because the groups were not matched on education (PSZ had 2 years less than HCS), we also examined the relationship between education and K. There was a strong positive correlation in HCS (memory load 3: r = 0.46, P = 0.04; memory load 5: r = 0.049, P = 0.03), such that those with higher K tended to have higher education. However, there was no significant correlation between K and education in PSZ (memory load 3: r=0.19, P=0.35; memory load 5: r=0.25, P=0.23). The most plausible explanation for this pattern of results is that better WM allows some healthy people to progress further than others in education, but that schizophrenia typically prevents people from attaining higher levels of education (irrespective of their WM capacity). There were no significant correlations between education level and CDA amplitude in HCS (memory load 1: r=0.33, P=0.14; memory load 3: r = 0.04, P = 0.87; memory load 5: r = 0.03, P = 0.89) or in PSZ (memory load 1: r=0.12, P=0.56; memory load 3: r=

| Table 3 Correlations between K and the WM domain score from the MATRICS battery | | | | | | |
|---|-------------|-----------------------|-------------------------|--|--|--|
| Group | Memory load | Pearson's r (P-value) | Spearman's rho (P-value | | | |
| HCS | 3 | 0.51 (0.03) | 0.29 (0.24) | | | |
| HCS | 5 | 0.49 (0.03) | 0.30 (0.22) | | | |
| PSZ | 3 | 0.53 (0.01) | 0.53 (0.01) | | | |
| PSZ | 5 | 0.36 (0.09) | 0.54 (0.01) | | | |

We also examined the potential impact of illness duration on our results. There was a strong negative correlation between K at memory loads 3 and 5 and illness duration (memory load 3: r = -0.41, P = 0.05; memory load 5: r =-0.48, P = 0.02). However, illness duration was highly correlated with age at the time of testing (r=0.93, P<0.001). In HCS, age at testing was significantly correlated with K (memory load 3: r = -0.56, P = 0.01; memory load 5: r =-0.61, P < 0.01), which matches many previous studies showing age-related declines in WM function (e.g., Park et al. 2002; Brockmole et al. 2008). In PSZ, illness duration was no longer correlated with K when the influence of age was partialled out (memory load 3: r = 0.26, P = 0.23; memory load 5: r = 0.26, P = 0.24). Thus, there was no evidence that illness duration per se influenced K. There was also no significant correlation between CDA amplitude and illness duration in PSZ (memory load 1: r = -0.3, P = 0.15; memory load 3: r =-0.20, P = 0.36; memory load 5: r = -0.36, P = 0.09).

Discussion

The main question addressed by this experiment was whether the pattern of neural activity in PSZ, who have been shown to have a reduced WM capacity (Gold et al. 2003, 2010), is similar to that of HCS who have similarly low WM capacity. The answer is clearly "no." The most direct evidence for this conclusion comes from the relationship between CDA amplitude and memory load, which was strikingly different between PSZ and HCS, even in analyses of subgroups that were matched for K. PSZ exhibited increased CDA amplitude relative to HCS for memory load 1 but tended to exhibit decreased CDA amplitude relative to HCS for memory loads 3 and 5. This pattern of results indicates that the neural mechanisms that produce a given level of WM performance are different for PSZ and HCS. Moreover, whereas we replicated previous studies showing that the change in CDA between low and intermediate memory loads is predictive of WM memory capacity in healthy individuals (Vogel and Machizawa 2004; Anderson et al. 2011), this correlation was absent in PSZ. In contrast, we found that larger CDA amplitudes at memory load 1 strongly predicted a drop in our behavioral measure of capacity, K, at memory load 5 in PSZ, whereas this relationship was absent in HCS. Thus, the typical pattern of neural activity is different in PSZ than it is in HCS, even for individuals with similar WM capacity, and the neural factors that accompany individual differences in WM performance are different in PSZ and HCS. Specifically, a primary source of WM variability in PSZ appears to be the mechanism that controls the amplitude of the CDA at memory load 1, whereas a primary source of WM variability in HCS appears to be the mechanism that controls the increase in CDA from memory loads 1 to 3.

The most striking effect in the present study was the larger CDA amplitude for PSZ than for HCS at memory load 1. An analogous pattern has been observed in the prefrontal blood oxygenation level-dependent signal (BOLD) during the performance of *N*-back tasks (see Manoach 2003 for a review). Specifically, PSZ showed increased BOLD activity at low loads (i.e., 1-back) relative to HCS, but decreased BOLD activity relative to HCS at high loads (i.e., 2- or 3-back). This was

Because the CDA reflects, in part, the selective maintenance of information from the to-be-remembered side relative to the to-be-ignored side, our results suggest that PSZ are more selective than HCS at memory load 1. This contrasts with previous work in healthy individuals showing that low Kis correlated with a failure to select among distractors (Conway et al. 2001; Bleckley et al. 2003; Vogel et al. 2005; McNab and Klingberg 2008). Thus, whereas low K in healthy individuals is associated with impaired selection, the lower Kof PSZ compared with HCS may reflect an opposite tendency to hyperfocus.

It should be noted that WM is a complex construct, and the change detection paradigm used in the present study provides a relatively pure measure of storage capacity over a very short duration, with minimal demands on maintenance or executive processes. Nevertheless, *K* was strongly correlated with the WM score from the MATRICS battery, indicating that it shares variance with the broader construct of WM. Other tasks that are widely used to measure WM capacity, such as the *N*-back and Sternberg tasks, require additional manipulation processes that are not captured by our *K* measure and may be disrupted in PSZ. Thus, the present study shows that PSZ exhibit a specific impairment in the storage of multiple object representations in WM, and additional research is needed to determine how this impairment is related to impairments in other components of the WM system.

We hypothesize that hyperfocusing exhibited by PSZ impairs their ability to maintain multiple simultaneous representations. Hyperfocusing on a single memory representation would not impair performance when there is only one object that should be stored in memory. At higher memory loads, however, a tendency to hyperfocus might lead PSZ to select a subset of the to-be-remembered objects, which would be deleterious to performance and lead to a reduced capacity estimate. Indeed, individual differences in our CDA measure of hyperfocusing (i.e., CDA at memory load 1) were strongly correlated in PSZ with a drop in behavioral performance when the memory load increased from 3 to 5. In other words, PSZ who were prone to hyperfocusing on the to-be-remembered side under low-load conditions also had greater difficulty in remembering all of the information from the to-be-remembered side when the memory load was high.

Although the idea that hyperfocusing can explain impaired WM capacity in PSZ is merely a conjecture at this point, the present findings converge with other recent results suggesting that PSZ have a general deficit when required to divide attention among multiple task-relevant sources of information, and that they tend to engage in abnormally enhanced selectivity under these conditions. First, spatial cuing studies have shown that PSZ exhibit no impairment in focusing attention onto a single location (Luck et al. 2006), but they are impaired when endogenously cued to attend to multiple locations (Elahipanah et al. 2011; Hahn et al. 2012). Another study has shown that PSZ are actually more effective than HCS at clearing an object from WM when it is no longer relevant

(Hahn et al. 2012). In addition, although it did not reach significance, a previous study found that the N2pc component a neural signature of attentional selection—was greater in PSZ than in HCS when attention was focused onto a single target object in a visual search task (Luck et al. 2006). Previous research suggests that similar mechanisms of attention may operate in both perception and WM (Awh and Jonides 2001; Kuo et al. 2011), suggesting the possibility that a specific deficit in schizophrenia could cause a widespread impairment across a range of seemingly disparate tasks. All of these results point to a deficit in simultaneously processing multiple sources of information—whether in perception or in WM and a tendency toward hyperfocusing on a subset of to-be-attended sources of information.

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Notes

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