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Differential effects of paced and unpaced responding on delayed serial order recall in schizophrenia

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ABSTRACT

Working memory for temporal order is a component of working memory that is especially dependent on striatal systems, but has not been extensively studied in schizophrenia. This study was designed to characterize serial order reproduction by adapting a spatial serial order task developed for nonhuman primate studies, while controlling for working memory load and whether responses were initiated freely (unpaced) or in an externally paced format. Clinically stable schizophrenia patients (n = 27) and psychiatrically healthy individuals (n = 25) were comparable on demographic variables and performance on standardized tests of immediate serial order recall (Digit Span, Spatial Span). No group differences were observed for serial order recall when read sequence reproduction was unpaced. However, schizophrenia patients exhibited significant impairments when responding was paced, regardless of sequence length or retention delay. Intact performance by schizophrenia patients during the unpaced condition indicates that prefrontal storage and striatal output systems are sufficiently intact to learn novel response sequences and hold them in working memory to perform serial order tasks. However, retention for newly learned response sequences was disrupted in schizophrenia patients by paced responding, when read-out of each element in the response sequence was externally controlled. The disruption of memory for serial order in paced read-out condition indicates a deficit in frontostriatal interaction characterized by an inability to update working memory stores and deconstruct 'chunked' information.

The ability to encode and briefly retain information in working memory, then recall that information to produce appropriate actions is a fundamental cognitive faculty critical to many aspects of everyday behavior. Verbal and spatial working memory deficits are well established in schizophrenia (Park and Holzman, 1992) (Reilly et al., 2007; Barch et al., 2001) and may underlie a wide range of cognitive deficits (Goldman-Rakic, 1991), functional impairments (Green, 2006), and clinical symptoms (Pantelis and Maruff, 2002).

Animal models have demonstrated a functional interdependence between dorsolateral prefrontal cortex and basal ganglia in working memory, especially when learned response sequences are enacted and require ongoing interaction between storage and retrieval processes (Barone and Joseph, 1989; Mushiake and Strick, 1995; Ninokura et al., 2004). Computational models suggest an essential role for dopamine tone in basal ganglia processing of serial order (Gruber et al., 2003), especially for learned motor responses. Output to basal ganglia can strengthen thalamic inputs to frontal cortex to support initiation of commands for learned motor responses both directly and indirectly (Frank et al., 2001). Specifically, selective dopamine-2 (D2) receptor mechanisms in the striatum disinhibit thalamocortical loops, thereby regulating motor output related to information maintained working memory systems (Frank et al., 2001; McNab and Klingberg, 2008). Altered thalamocortical drive to prefrontal cortex could destabilize maintenance of coherent cell firing and subsequently, lower signal to noise in prefrontal working memory systems to cause faster decay of information over delay intervals and enhanced vulnerability to destabilization from distracting cues or competing demands.

One critical aspect of working memory is to preserve information and bind behavioral plans over time. Performing serial order response tasks requires working memory processes, especially before response sequences are practiced and overlearned, at which time the basal ganglia plays a greater role via procedural learning mechanisms. However, serial order processing has received relatively little attention in the schizophrenia literature. Studies using span-type tests, such as Corsi blocks, to assess immediate recall of spatial serial order generally report encoding and retrieval deficits in schizophrenia (Lee and Park, 2005). In one study, impairments were exacerbated by a delay period (Dreher et al., 2001), suggesting that retrieval deficits

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were complicated by signal degradation during retention as has been reported in oculomotor working memory studies (Reilly et al., 2006). Proposed explanations for serial order deficits in schizophrenia have centered on forgetting (signal degradation) and interference (Fraser et al., 2004). Support for the vulnerability of serial order encoding and retention to interference during encoding comes from the "sandwich effect" (Hitch, 1975), in which irrelevant items are interleaved with target stimuli during presentation. A number of studies have reported exacerbated working memory deficits when distracting stimuli were present during encoding (Cellard et al., 2007) (Corrigan and Green, 1991) and retention (Reilly et al., 2007). There is also the possibility that limited capacity systems destabilize when saturated (Elvevåg et al., 2002). Indeed, serial order recall deficits emerge in schizophrenia when sequence length increases from three to five items (Dreher et al., 2001) and vulnerability to distraction is enhanced as function of sequence length (Cellard et al., 2010). Overall, there is mounting evidence for serial order processing deficits in schizophrenia, both in verbal and non-verbal domains (Guérard and Tremblay, 2008).

Typically studies of serial order processing vary the level of distraction and/or the amount of information to be processed. In schizophrenia research no prior study has examined the vulnerability of serial order processing to increased demands for frontostriatal communication by comparing free recall of a "chunked" response sequence vs. cued serial retrieval of each item in a sequence. In lieu of adding distracting stimuli or processing demands, we introduce a novel paradigm designed to assess the vulnerability of spatial serial order retrieval to interference from coordination and output of sequences. By externally cueing item retrieval, repeated updating and read-out of a sequence is necessary and entails increased interaction of retrieval and storage systems in frontostriatal circuits. To this end, we adapted a spatial serial order recall task, developed for primate studies (Barone and Joseph, 1989) and varied the type of responding (unpaced vs. paced). To evaluate the interplay between saturation and internal interference from frequent readout and updating, we sampled a range of response set-sizes.

1. Methods

1.1. Participants

The patient sample included of 27 individuals who met criteria for schizophrenia spectrum disorders (24 schizophrenia; 3 schizoaffective) based on the Structured Clinical Interview for DSM-IV (SCID). To limit effects of both acute illness and recent changes to medication treatments, all patients were clinically stable, meaning there was no acute symptomatology, significant change in positive symptom severity, or change in pharmacotherapy regimen during the prior month. All patients were treated with either second-generation (n = 23) or first-generation (n = 4) antipsychotics. Concomitant medications included SSRIs (n = 3), mood stabilizers (n = 2), lithium (n = 1), anti-cholinergics (n = 1), and benzodiazepine (n = 1). A sample of 25 healthy individuals, recruited from the community via local advertisements and a research registry, were free of Axis I diagnosis based on SCID interviews. All participants had normal range intelligence (SS > 79) and were free of substance abuse within the last three months, lifetime history of substance dependence, neurological disease, head injury with loss of consciousness, and systemic disorders known to affect brain function. Written consent was provided by all participants and the study was approved by the Institutional Review Board at the University of Illinois at Chicago. As shown in Table 1, there were no group differences for age, education, parental socio-economic status, estimated premorbid intelligence, and current intelligence.

Table 1
Group demographic characteristics and clinical data (for schizophrenia group).

	Healthy Comparison (CTL) n = 25	Schizophrenia (SZ) n = 27	Analysis		
			F/χ^2	df	p
Demographics					
Age (years)	39.44 (10.94)	35.00 (9.98)	2.34	1,50	0.13
Sex					
Male	56.0%	66.7%	0.62	1	0.43
Female	44.0%	33.3%			
Race					
Caucasian	24.0%	22.2%	0.77	2	0.68
African-American	60.0%	51.9%			
Asian/Latino/Other	16.0%	25.9%			
Dominant hand					
Right	88.0%	96.3%	1.26	1	0.26
Left	12.0%	3.7%			
Education	13.80(1.83)	14.57(3.24)	1.10	1,50	0.30
Parental SES	3.20(1.19)	3.12(0.99)	0.08	1,49	0.78
WRAT-III: reading	95.17(12.16)	98.30(14.11)	0.71	1,49	0.40
WASI IQ[a]	101.36(11.07)	102.00(14.72)	0.03	1,50	0.86
Clinical data					
Illness duration (years)		11.85(10.78)			
PANSS total		38.00(6.57)			
PANSS positive		17.73(4.06)			
PANSS negative		19.27(5.16)			
Side effect ratings					
AIMS total		0.80(1.32)			
ESRS total		4.07(4.37)			

WRAT-III: Wide Range Achievement Test: Third Edition.
WASI: Wechsler Abbreviated Scale of Intelligence.
PANSS: Positive and Negative Syndrome Scale.
AIMS: Abnormal Involuntary Movement Scale.
ESRS: Extrapyramidal Symptom Rating Scale.
[a] WASI 2-subtest estimate of Full Scale IQ based on Vocabulary and Matrix Reasoning.

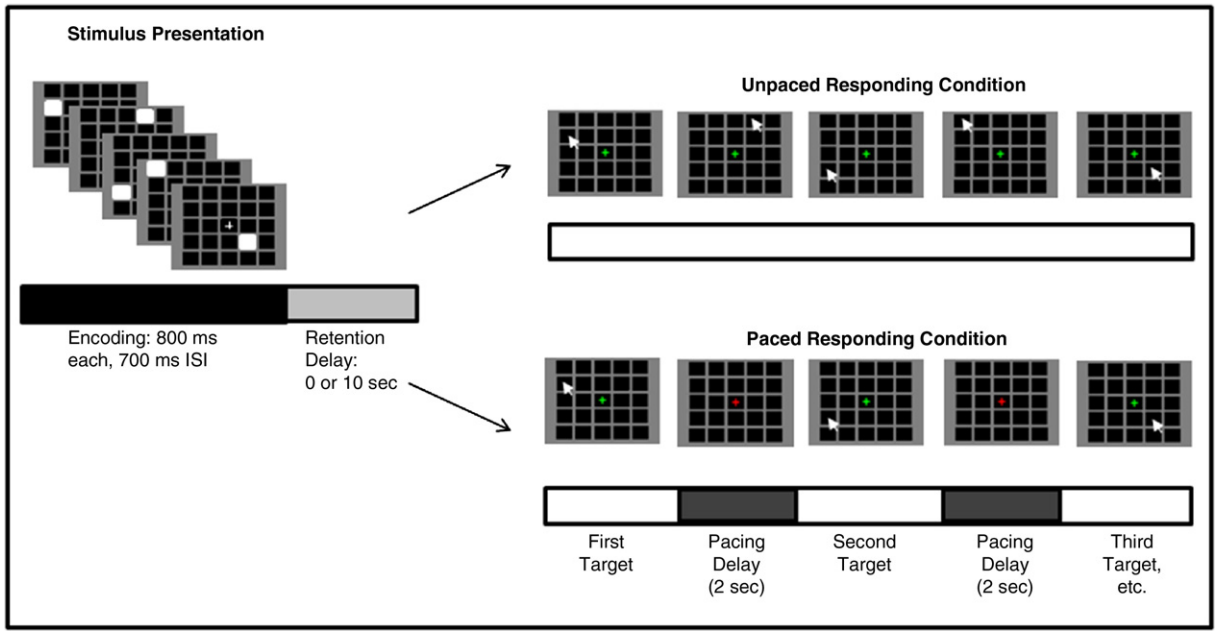

Fig. 1. The translational serial order recall paradigm was comprised of three components: Encoding, Delay, and Recall. *Encoding*. During encoding white targets were presented against a gray background on a 5×5 grid. The center location was never used as a target and no location was repeated in a trial. Targets were presented psuedorandomly (no two consecutive targets could be adjacent) and the encoding phase varied from 2300 ms (two item sequence) to 6800 ms (five item sequence). Participants were instructed to remember the location and order of each item. *Delay*. In the no delay condition, recall followed encoding immediately. This condition was used to assess serial order recall with fewer demands placed on working memory systems. A retention delay condition of 10 s was used to robustly engage rehearsal systems. *Recall*. Two response output conditions were employed to assess the potential interference of deconstructing serial order. In the unpaced condition, when the central fixation turned green participants were asked to generate the complete sequence by clicking on the target locations in order at their own speed. In this condition there was no experimentally imposed delay between recall of serial order targets. In the paced responding condition, the central fixation turned red after the first selection was made and a two second pacing delay was imposed. Participants were cued to select the next item in serial order when the central fixation again turned green and the cursor re-appeared. Unlike n-back tests that require rapid updating and rapid responding, there was no fixed time limit for responding once the go cue (green fixation) appeared. Additionally, whereas n-back tests are characterized by a steep incline in difficulty level when progressing from 0-, to 1-, to 2-back conditions, the present task employed a more gradual increase in difficulty from working memory loads of 2 items in order up to sequences of 5 items.

1.2. Spatial serial order paradigm

Based on animal models of serial order recall (Barone and Joseph, 1989) and recent schizophrenia findings (Fraser et al., 2004), we adapted a spatial serial order paradigm. This task required participants to remember the position and serial order of targets presented on a 5×5 grid. The center of the grid was a central fixation point and was never used as a target. Targets were presented psuedorandomly and participants were instructed to remember the item location and order. In the unpaced response condition, participants were asked to generate the complete sequence at their own speed by clicking on target locations. In the paced responding condition, a two second pacing delay was imposed after each response, then participants were cued to click on the next location in the series (see Fig. 1). Similar methodology has been used in neurophysiological studies with nonhuman primates to delineate frontostriatal integration during serial order recall. The processing demand was manipulated for both unpaced and externally paced trials by randomly varying number of to be remembered locations (2 to 5 item sequences).

1.3. Procedures, data processing, and statistical procedures

The translational spatial serial order task was run on a 15.4 in. laptop screen using E-Prime software (Schneider et al., 2002). To reduce the potential for paced instructions to interfere with performance during the unpaced condition, the two conditions were administered in separate sessions on separate days with the unpaced condition always administered first. Should different strategies be employed one would expect differential reaction times for comparable response segments, yet no reaction time differences were observed across the two conditions for latency to first click, latencies between unpaced responses, or latencies following pacing delays (see Fig. 1). Repeated measures ANOVA were computed for accuracy with response type, retention delay, and processing load as within-subjects variables while diagnosis (patients vs. healthy controls) was the between-subjects variable. To further assess encoding and immediate retrieval in the context of serial order processing, two additional neuropsychological measures were administered including the Digit Span and Spatial Span from the Wechsler Memory Scale-Third Edition (WMS-III). Mean comparisons for neuropsychological measures were conducted using one-way ANOVA.

2. Results

2.1. Standardized span tests

No group differences were observed for immediate serial order recall on standardized neuropsychological tests between these IQ matched groups on either the Digit Span [$F(1,50)=0.12$, $p=.73$] ($SZ=18.56\pm4.78$; $HC=19.00\pm4.54$) or Spatial Span tests [$F(1,50)=0.19$, $p=.66$] ($SZ=13.48\pm3.19$; $HC=13.08\pm3.38$). Furthermore, when forward and backward span was examined separately, there were no group differences on either the Digit Span or Spatial Span tests (see Supplementary Materials). Correlations were computed for Spatial Span forward and backward with the paced and unpaced conditions of the translational serial order recall test. For the control group all four conditions (Spatial Span forward and backward, paced and unpaced responding) were significantly correlated ($r=.66$ to $.71$). In the schizophrenia group Spatial Span forward was significantly correlated with performance on the translational task ($r=59$ to $.60$), however, backward span was uncorrelated with either condition on the translational task.

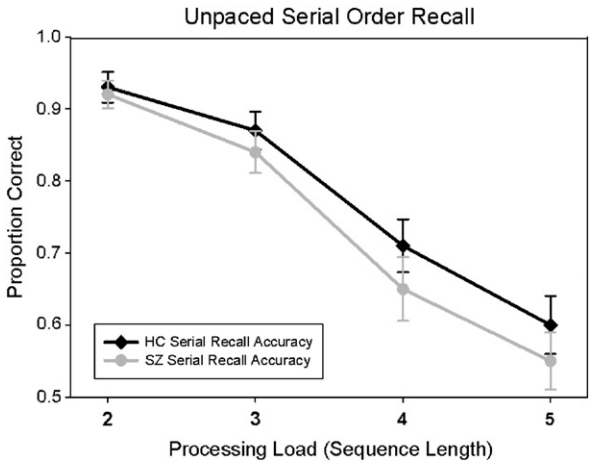

Fig. 2. There were no group differences when serial order recall was unpaced regardless of whether a 10 s rehearsal delay was imposed prior to initiating recall. These findings were consistent with the lack of group differences on standardized span measures and intelligence. Furthermore, this pattern of performance suggests that frontostriatal systems are sufficiently intact in schizophrenia to learn novel sequences and hold them in recurrent loops to perform immediate and delayed unpaced serial recall tasks.

2.2. Translational serial order test

A four-way repeated measures ANOVA was used to assess the impact of diagnosis (schizophrenia vs. control group), retention delay (immediate recall vs. recall after 10 s delay), type of response output (paced vs. unpaced responding), and processing load (sequence length 2–5) on recall accuracy of the translational serial order recall test. There were significant main effects for response output [$F(1,50) = 45.25$, $p < .001$] and retention delay [$F(1,50) = 33.19$, $p < .001$], while diagnosis [$F(1,50) = 3.79$, $p = .057$] was marginal and processing load [$F(3,48) = 0.27$, $p = .84$] was nonsignificant. Significant two-way interactions included response type by diagnosis [$F(1,50) = 6.63$, $p = .01$], response type by retention delay [$F(1,50) = 64.69$, $p < .001$], response type by processing load [$F(3,48) = 3.77$, $p = < .02$], and retention delay by processing load [$F(3,48) = 4.78$, $p < .01$]. The three-way response type by diagnosis by processing load interaction for was significant [$F(3,48) = 3.02$, $p < .04$] was significant, but neither the four-way nor any other three-way interactions were significant. The three-way interaction was clarified by collapsing retention delay and processing load to test for group differences in response output conditions using separate univariate ANOVA. There was no deficit in patient performance when responding was unpaced [$F(1,50) = 0.98$, $p = .33$] (for illustrative purposes, processing load was provided on the horizontal axis in Figs. 2 and 3). Thus, matched performance was observed on both standardized neuropsychological and translational measure serial order encoding and recall of sequences, regardless of processing load or presence of a retention delay. Fig. 3 shows that accuracy for serial recall was significantly impaired in schizophrenia patients as a function of externally pacing the response output, regardless of processing load or presence of a retention delay [$F(1,50) = 4.46$, $p < .05$].

2.3. Error analysis

Errors were classified into three main types: omissions, transpositions, and intrusions (Guérard and Tremblay, 2008; Henson, 1998). An omission occurs when the participant fails to produce a response. There were very few omission errors, thus omissions were not included in the error analyses. A transposition error occurs when a target location is selected in a different serial position. An adjacent error was defined as an incorrect spatial location immediately adjacent (above, below, or to either side) to the target. This error type was conceptualized as the visual–spatial counterpart to Henson's (1998) verbal confusion error in which an incorrect letter was phonologically similar to the correct item. Finally, ordinary intrusion errors were incorrect items that were not near the target location (adjacent errors) and not transpositions. Note that target sequences were constrained such that there was no opportunity for adjacent errors to overlap with a transposition error. For error analysis we examined only trials with sequences greater than two spatial locations. Because of the relatively low number of errors and categorical data, a chi-square analysis was used to assess whether error type was disproportionate across the response output conditions (paced vs. unpaced) in the schizophrenia group. There was no significant difference in the frequency of either adjacent (unpaced: 42.5% vs. paced: 38.3%) or intrusion (unpaced: 30.8% vs. paced: 24.3%) errors. However, the proportion of transposition errors was significantly greater ($\chi^2 = 4.29$, $df = 1$, $p < .05$) when response output was paced (37.4%) vs. unpaced (26.7%) (Fig. 4).

3. Discussion

This is the first investigation to utilize serial order processing tasks to assess the role of controlled response output and retention delay on serial order recall in schizophrenia. In groups of demographically similar schizophrenia patients and psychiatrically healthy controls, no patient deficit was demonstrated in unpaced response output conditions either on standard neuropsychological tests of immediate sequence recall (Digit Span & Spatial Span: forward & backward) or serial order recall during the unpaced responding condition. Thus, when novel response sequences could be read out as a unit, performance was not significantly impaired. In contrast, performance deficits were observed when response output was externally paced so that items in a response series were read out individually rather than as a group or "chunk". These findings indicate that prefrontal storage and striatal output systems are sufficiently intact to learn novel response sequences and hold them in working memory to perform serial order tasks. These findings do not indicate a rapid decay of stored serial response information in working memory, the observed deficits suggest that serial order storage becomes susceptible to

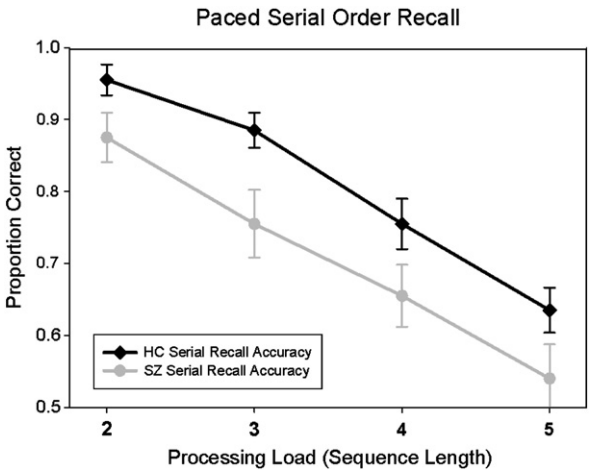

Fig. 3. Accuracy for serial order recall was significantly impaired in schizophrenia patients when response output was externally paced. Regardless of whether sequence recall was initiated immediately after encoding or after a 10 s delay, patient performance suffered when they were required to wait two seconds between sequence elements rather than reading out the entire sequence at once. These group differences were observed in the context of comparable group demographics, similar levels of estimated intelligence, and unpaced serial order recall. Thus, the present findings suggest a selective deficit of frontostriatal systems in schizophrenia in addition to generalized cognitive deficits which often characterized the disorder.

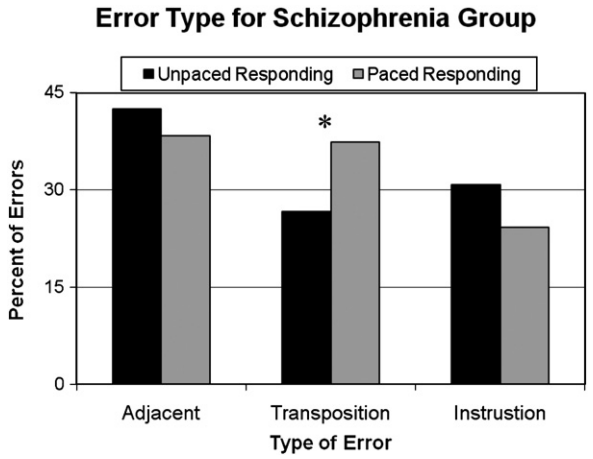

Fig. 4. Accuracy was significantly impaired in the schizophrenia group for paced compared to unpaced serial order recall. To further evaluate the nature of this decline, an analysis of error type was undertaken. Compared to stable levels of adjacent (spatial-location) and ordinary intrusion errors across response output conditions, schizophrenia patients displayed significantly more transposition errors in which target locations were selected out of order. This suggests that serial order, not item location, is disrupted by pacing responding one item at a time rather than all at once.

disruption when responding is externally controlled. Indeed, as opposed to prior studies utilizing cognitively demanding tasks which may "crowd out" the retention elements, (Cellard et al., 2007; Corrigan and Green, 1991; Elvevåg et al., 2001) the present study showed that merely reading out a sequence in a highly controlled manner was sufficient to disrupt recall.

Prior studies have reported impaired performance on span and other serial order recall tests in schizophrenia (Dreher et al., 2001; Fraser et al., 2004; Silver and Goodman, 2008; Goldberg et al., 1998), yet the present findings indicated intact performance on several aspects of serial order recall when schizophrenia patients were demographically similar to psychiatrically healthy participants, particularly on measures of general cognitive ability. Discrepancies in methodologies and sampling issues may be responsible for such apparent contradictions. That is, prior studies of delayed spatial serial recall may be confounded by general cognitive deficits in the patient groups as no previous investigation of delayed spatial serial order recall has matched patients and controls on premorbid intellectual level or current cognitive abilities. The present study was designed to recruit a healthy comparison group that was demographically similar to the schizophrenia sample on a variety of measures including general cognitive ability (Table 1). Compared to prior studies, this sample of schizophrenia patients may be higher functioning and there was no history of learning or cognitive problems in the control group. Against this background of similar premorbid and current intellectual abilities as well as matched performance on measures of unpaced serial order recall, the present findings suggest a specific vulnerability of serial order processing to disruption which goes beyond generalized deficits in schizophrenia.

Although sampling issues may partially account for the divergence of the present findings from prior studies of spatial serial order recall, there is ample evidence of spatial working memory deficits across a wide range of working memory paradigms and patient samples (Lee and Park, 2005). One explanation is that separately accessing each item in a learned sequence degrades the memory trace of the response series maintained in prefrontal working memory systems. Activation of prefrontal neurons during delay periods is essential for maintaining information (Goldman-Rakic, 1999) and selective prefrontal activity has been observed during serial order recall in primates (Barone and Joseph, 1989; Kermadi and Joseph, 1995). If activity drops over time due to retrieval of individual items, then a new or competing stimulus could displace the serial information as to what is maintained. The present data are consistent with the notion that paced responding either displaces the target sequence directly or reduces maintenance activity such that other stimuli could displace the sequence. In the healthy control group maintenance of target sequences might be more robust to such disruptions as intrinsic excitation (Miller et al., 1996) facilitates recovery of the relevant information after competing stimuli are briefly represented by prefrontal working memory neurons. In contrast, the contents of working memory are clearly disrupted or displaced in schizophrenia and the ability to intrinsically recover working memory stimuli after this brief disruption appears impaired. There are a number of possible mechanisms that could account for intrinsic recovery of previously maintained information (Durstewitz et al., 2000; Gorelova and Yang, 2000; Lewis and O'Donnell, 2000) and these models are consistent with the notion that, in schizophrenia, the mere act of accessing serial order information accelerates the degradation of working memory stores to a level below the threshold for intrinsic recovery.

3.1. Frontostriatal communication

Another explanation is that this serial order recall paradigm uniquely assesses the interaction between prefrontal maintenance systems and motor output systems in the basal ganglia. The present task entails motor sequence learning, hence greater basal ganglia involvement and feedback than is typical of working memory paradigms. Anatomical connections from prefrontal cortex to the basal ganglia, thalamus, and back to the prefrontal regions form a "loop" that detects, encodes, and maintains serial order information (Barone and Joseph, 1989; Kermadi and Joseph, 1995). These recurrent loops are relatively private (Inase et al., 1996; Kelly and Strick, 2003; Middleton and Strick, 1997) and may account for the high degree of functional integration within serial order working memory circuits (Houk et al., 2007). The interaction between frontal cortex and basal ganglia in the service of working memory has been modeled as a division of labor in which prefrontal cortex uses continuous firing to maintain information over time whereas the role of the basal ganglia is to update the contents of working memory via selective firing (Frank et al., 2001). Thus, the observed vulnerability of sequence read-out may indicate disrupted communication between prefrontal storage systems and basal ganglia signaling systems. That is, prefrontal systems are unable to comply when portions of the sequence that have become irrelevant and must be discarded.

The basal ganglia participate in a wide range of cognitive processes by interacting with multiple areas of frontal cortex (Alexander et al., 1986) and may play a significant role in processing serial order. Recent findings suggest a unique role for dopamine systems in the basal ganglia, particularly the caudate, in support of working memory. For example, striatal dopamine synthesis has been reported to predict working memory capacity (Cools et al., 2008). More specifically, caudate dopamine has been correlated with working memory processing speed (Landau et al., 2009) and basal ganglia activity predicts the extent to which relevant information is gated and stored in working memory (McNab and Klingberg, 2008). Together these findings indicate a critical role for the caudate in detecting context changes that trigger updates to working memory contents (Badgaiyan et al., 2007) and gating of prefrontal activity. The present task requires one to cleave a target item from the full sequence when that item is no longer relevant. The finding of reduced accuracy during paced output of serial order may reflect an attenuated caudate signal for updating working memory. Insufficient updating in which the irrelevant sequential items are not discarded may increase competition among items in serial order, thereby leading to more transposition errors (without disrupting memory for item location). Future studies distinguishing order reconstruction and serial order recall in the context of paced and unpaced responding may clarify this issue.

Regardless, the observed error pattern of significantly more sequential errors during paced responding may indicate more prominent striatal feedback dysfunction in schizophrenia than previously theorized. The present findings also build on models of the interaction between basal ganglia and prefrontal cortex (Frank et al., 2001) and the idea that the caudate plays a crucial role in both detecting changes in context and triggering updates to working memory. Clearly, more direct assessments of caudate function in this context are needed to support this notion.

Because the paced serial order recall condition included two second pacing delays between each response, the maintenance duration was longer when compared to the unpaced condition. Thus, participants were required to hold the tail end of a sequence longer during the paced condition, and the longer delays may hasten the degradation of the working memory trace. Should this be the case, one would expect an increased demand on maintenance processing sufficient to produce an exaggerated recency effect during paced responding. However, there was no evidence of differential error rate in either the paced or unpaced condition as a function of serial position. Another potential limitation is the impact of chronic exposure to antipsychotic treatments. The majority of patients had an extensive history of treatment with antipsychotic medication, thus it is difficult to disentangle disease effects from chronic treatment effects. This will be an important issue to address in future studies considering the critical role that dopamine plays in both prefrontal maintenance and caudate signaling for updates to working memory stores.

Supplementary materials related to this article can be found online at doi:10.1016/j.schres.2011.04.024.

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Contributors

Peter Weiden, MD: subject recruitment services.

Ellen Herbener, PhD: clinical ratings and independent diagnostic evaluations.

Conflict of interest

There are no conflicts of interest to report.

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