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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.