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The Effects of Perceptual Encoding on the Magnitude of Object Working Memory Impairment in Schizophrenia

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Abstract

Deficits in the visual working memory (WM) system have been consistently reported in schizophrenia patients, but the relative contribution of initial perceptual encoding to these deficits remains unsettled. We assessed the role of visual perceptual encoding on performance on an object WM task. Schizophrenia patients (N=37) and nonpsychiatric control subjects (N=33) were tested on an object WM task involving three delay periods: 200 msec, 3 sec, and 10 sec. Schizophrenia patients performed significantly less accurately than controls on all three conditions. However, after controlling for the effect of perceptual encoding (accuracy on the 200 msec delay condition) on performance in the two memory load conditions, schizophrenia patients demonstrated intact WM in the 3 sec delay condition, and showed a weak trend for decreased accuracy on the 10 sec delay compared with controls. Analysis of individual differences in pattern of performance revealed that a distinct subgroup of poor encoder patients had a significantly greater reduction in accuracy at 3 sec than the other patient subgroups and controls. In contrast, among schizophrenia patients who performed poorly on the 10 sec delay, accuracy was equivalently reduced independent of encoding ability. WM deficits in controls were independent of encoding ability at both delay intervals. These results indicate that encoding ability titrates the magnitude of WM impairment in schizophrenia patients but not in controls, and that heterogeneity has to be taken into account to correctly estimate the effects of perceptual encoding on visual object WM deficits in schizophrenia.

INTRODUCTION

Working memory (WM) is a limited-capacity, short-term storage system for maintaining mental representations “online” for further processing in the service of response selection (Goldman-Rakic, 1992, Miyake and Shah, 1999) (Baddeley, 1986, Baddeley, 1992). An extensive research literature has confirmed that impaired WM is a cardinal feature of schizophrenia (Goldman-Rakic, 1991, Park and Holzman, 1992b, Keefe et al., 1995, Servan-Schreiber et al., 1996, Gold et al., 1997, Spindler et al., 1997, Coleman et al., 2002, Gold et

Contributors

Michael Coleman and Deborah Levy conceived of the study, designed it, and wrote the manuscript. Olga Krastoshevsky carried out the study and wrote the manuscript. Xiawei Tu and Nancy R. Mendell analyzed the data and contributed to the interpretation.

Conflicts of Interest

The authors report no conflicts of interest.

al., 2010). Meta-analytic studies have found that WM deficits in schizophrenia are present in all modalities, across diverse methodologies, and are not accounted for by differences in IQ between patients and control subjects (Lee and Park, 2005, Forbes et al., 2009). Neuroimaging studies report abnormal neural activity during WM tasks in schizophrenia patients (Callicott et al., 2000, Barch et al., 2001, Barch et al., 2002, Kim et al., 2003, Manoach, 2003) and their unaffected first-degree relatives (Callicott et al., 2003). Further, neural circuits and neurotransmitter systems known to be abnormal in schizophrenia patients, particularly involving prefrontal dopamine, play key roles in WM processes; dysfunction in these systems is hypothesized to underlie WM deficits in schizophrenia (Goldman-Rakic, 1991, Barch, 2004, Seamans and Yang, 2004, Lisman et al., 2008). WM is critically involved in learning, problem solving, decision-making, anticipation, planning, and other cognitive functions that are frequently impaired in schizophrenia patients and is implicated in multiple neuropsychological deficits (Goldman-Rakic, 1994, Green, 1996, Silver et al., 2003).

Although most WM studies have focused on maintenance and executive processes (Callicott et al., 2000, Barch et al., 2001, Manoach, 2003), behavioral (Tek et al., 2002, Gold et al., 2003, Hartman et al., 2003, Lencz et al., 2003, Kim et al., 2006, Javitt et al., 2007), fMRI (Haenschel et al., 2007) and electroencephalographic (Haenschel et al., 2007, Dias et al., 2011) evidence also implicates abnormal encoding in WM impairments in schizophrenia patients. Much of the evidence for the role of impaired encoding in visual-spatial WM has come from delayed response (DR) and delayed match to sample (DMTS) tasks. The effects of encoding can be separated from the effects of maintenance and retrieval by comparing performance on 0-delay (i.e., testing memory immediately after the stimulus is removed) or non-memory (i.e., the stimulus remains present throughout the trial) conditions with longer delay conditions (i.e., ≥ 3 sec). Such designs do not always find evidence of impaired encoding in schizophrenia patients, possibly because ceiling effects may obscure underlying deficits in the patient group (Park and Holzman, 1992a, Javitt et al., 1997, Snitz et al., 1999). The fact that lengthening the delay interval beyond 1 second does not change the magnitude of performance differences between patients and controls implicates a role for encoding in impaired WM (Lee and Park, 2005).

In this study we assessed the role of visual perceptual encoding on performance on an object WM task. We measured encoding accuracy on a 200 msec delay interval in order to separate the effects of initial encoding from WM performance on 3 sec and 10 sec delay intervals. We hypothesized that perceptual encoding would be impaired in schizophrenia patients and would contribute to deficits in WM performance on the 3 sec and 10 sec delay intervals. We further hypothesized that worse performance would be observed in schizophrenia patients on the 3 sec and 10 sec delay intervals even in the absence of deficits in perceptual encoding. In addition, we examined whether inter-individual differences in performance across the 3 conditions could clarify discrete encoding and maintenance impairments.

Materials and Methods

Participants

The subject groups included 37 patients who met Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition) (DSM-IV) criteria for a diagnosis of schizophrenia or schizoaffective disorder (SZ) and 33 NC subjects (American Psychiatric Association, 1994). Demographic characteristics of the sample are presented in table 1. The groups did not differ in age, years of education, or familial socioeconomic status (SES) (Hollingshead and Redlich, 1958, Hollingshead, 1965). The schizophrenia group had a slightly larger proportion of males than the controls. NC participants had a higher mean estimated verbal IQ based on the vocabulary subtest of the Wechsler Adult Intelligence Scale-Revised

(WAIS-R) (Wechsler, 1981). The patients were chronically ill outpatients (mean duration of illness = 16.7 years, SD = 8.8) and were moderately symptomatic as measured by the Brief Psychiatric Rating Scale (BPRS) (Overall and Gorham, 1962) (M = 44.7, SD = 15.1). The mean chlorpromazine-equivalent dose for the patients was 445 ± 249 mg/day (range = 198-990) (Davis, 1974, Woods, 2003). The NC group was restricted to individuals who did not meet *DSM-IV* criteria for any psychotic disorder (lifetime), bipolar disorder without psychotic features, or a schizophrenia-spectrum personality disorder, and who had no family history of psychosis, suicide, or psychiatric hospitalizations. Axis I disorders were assessed using the Structured Clinical Interview for *DSM-IV*, Patient Edition (Spitzer et al., 1994). Schizotypal, schizoid, and paranoid personality disorders were assessed in NC subjects using the Structured Interview for Schizotypal Symptoms (Version 1.5) (Kendler, 1989). An experienced clinician administered the interviews, and an independent group of senior diagnosticians reviewed the interview material and all available hospital records and assigned consensus diagnoses based on best estimate methods (Leckman et al., 1982). The interviews and diagnostic evaluations were performed blind to the experimental procedures and group membership. The following exclusion criteria applied to all participants: (a) lack of fluency in English; (b) history of serious head trauma or diagnosed organic brain disease; (c) history of substance abuse or dependence during the past 2 years or previous chronic dependence. All participants provided written informed consent and were paid for their participation.

Task and Stimuli

Participants were tested on an object recognition WM task that utilized complex visual stimuli chosen to minimize mneumonic strategies or verbal recoding of the stimuli. The stimuli were administered using a personal computer equipped with an 18-in monitor (45.7 cm) and a serial response box (Psychology Software Tools, Inc., Pittsburgh, PA). The task (Figure 1) was presented using a DMTS object WM paradigm. Subjects were presented with a target object, a grayscale image of a snowflake (Bentley and Humphreys, 1962) and were instructed to remember the object. The task employed three delay periods: a 200 msec (baseline) delay designed to tap initial perceptual encoding, and two WM conditions, a 3 sec, and a 10 sec delay period. The task was presented in three blocks of 40 trials each, organized by delay period. The order of presentation of the three blocks was semi-randomized.

To begin the experiment, subjects were presented with a brief prompt (“press the spacebar to begin”) followed by a target snowflake that was centrally illuminated on the computer screen for 250 msec and then replaced by a cross upon which subjects were instructed to fixate during the delay period. After the delay period, a second snowflake (probe) was illuminated on the computer screen, and subjects were instructed to indicate whether the probe snowflake was the same as the target snowflake by pressing a “Yes” or a “No” button on the response box. The probe remained on the screen until a response was made or 10 seconds elapsed. The target and probe snowflakes subtended about 13° of visual angle.

Statistical Analyses

The dependent measure for WM accuracy was the proportion correct score (# of correct responses/ # of trials). Planned comparisons between and within groups were carried out using Wilcoxon rank sum and signed-rank tests, respectively. Glass’ estimates of effect size (es) were calculated (Hedges, 1981). Repeated measures analysis of variance (ANOVA) was used to determine the effects of perceptual encoding ability on performance on the WM delay intervals.

Results

Summary statistics for accuracy scores of the two groups for the three delay intervals are presented in table 2. Schizophrenia patients were significantly less accurate than NC on all delay intervals: 200 msec (Z=2.97, P=0.003, es:1.27); 3 sec (Z=3.18, p=0.002, es:1.0); 10 sec (Z=3.77, P=0.0002, es:1.0). Both subject groups showed a significant decline in performance on the 3 and 10 sec delay intervals (table 2, figure 1 of supplementary materials) compared with the 200 msec perceptual encoding condition. Performance did not differ significantly between the 3 sec and 10 sec delay intervals in either group (SZ: S=54, P=0.2, es: 0.3; NC: S=105.5, P=0.1, es:0.17).

In order to separate the effects of perceptual encoding from the effects of maintenance and retrieval in the two delay conditions, we calculated change-from-perceptual encoding scores for both intervals: (3 sec accuracy - 200 msec accuracy; 10 sec accuracy - 200 msec accuracy). When perceptual encoding was accounted for in this fashion, patients did not differ significantly in accuracy from NC in the 3 sec delay condition (Z=-1.26, P=0.21, es: 0.39), a three-fold reduction in effect size suggesting that perceptual encoding had accounted for their poorer average accuracy on the 3 sec delay. Patients tended to be less accurate than NC in the 10 sec delay condition (Z=−1.90, P=0.06, es:0.47), indicating that the longer interval was more taxing on WM maintenance and retrieval capacities of patients. Accuracy did not change significantly within either group between the 3 and 10 sec delay intervals when baseline performance was taken into account (P's >0.1; SZ es:0.3; NC es: 0.04). These results are consistent with the finding that accuracy in the 3 sec (r=0.54, n= 70, P<0.0001) and 10 sec delay conditions (r=0.54, n= 70, P<0.0001) were correlated with accuracy in the 200 msec condition (r=0.54, n= 70, P<0.0001).

We set a cut-off for good versus poor performance after inspecting the distributions of accuracy scores (figures 2a, 2b). The maximum difference between the groups occurred at 90% accuracy in all conditions, with NC having more subjects (76%) with ≥90% accuracy at 200 msec than did patients (49%) [X^2 =5.4, df=1, P=0.02]. Accuracy scores on the 200 msec delay condition of ≥ 90% were used to distinguish good encoders from poor encoders (<90%).

Inspection of the individual data points revealed three distinct subgroups: 1) poor perceptual encoders with poor accuracy at 3 sec (16/34 or 47% of patients; 7/32 or 22% of NC), 2) good encoders with poor accuracy at 3 sec (15/34 or 44% of patients; 11/32 or 34% of NC), and 3) good encoders with high accuracy at 3 sec (3/34 or 9% of SZ; 14/32 or 44% of NC). The accuracy score means and standard deviations and samples sizes for the 3 and 10 sec delay conditions are reported for each group in Table 3 (see also figures 2 and 3 of supplementary materials). Among patients with impaired accuracy at 3 sec, poor encoders (n=16) performed worse than good encoders (n=15) (Z=2.421, P=0.02). Among both patients and controls, good encoders with good accuracy had equivalent mean values (NC: mean =0.95, SD=0.03, n=14; SZ: mean=0.92, SD=0.03, n=3).

Among NC with impaired accuracy at 3 sec, however, accuracy was identical independent of encoding ability (Z=0.05, P=0.96). Importantly, accuracy was equivalently compromised in patients and NC with good initial encoding but impaired performance at 3 sec (Z=−0.31, P=0.75). Thus, the group difference in performance on the 3 sec delay interval seems to be due to a distinct subgroup (n=16, 47%) of patients with impaired perceptual encoding.

A similar analysis was done after forming the same subgroups for the 10 second delay condition. These results are also reported in Table 3. Among patients who performed poorly at 10 sec, accuracy was equivalently reduced independent of encoding ability (Z=0.67, P=0.50), suggesting that factors related to the increased duration of the retention interval

played a greater role than perceptual encoding ability in poor WM performance (Table 3). However, among NC who performed poorly at 10 sec, good encoders (n = 13) tended to be less impaired than poor encoders (n = 5) (Z=−1.75, P=0.08), suggesting a facilitative effect of good encoding for meeting the increased retention demands. The only significant difference between patients and NC on the 10 sec delay occurred in subjects with good encoding but impaired 10 sec accuracy. Schizophrenia patients who were good encoders (n = 15) were more impaired than NC (n = 13) who were good encoders (Z=2.11, P=0.04), providing further support for the notion that factors other than encoding ability contribute to poor patient performance at longer delay intervals. Patients and controls with poor perceptual encoding and poor accuracy at 10 sec did not differ in accuracy (Z=−0.07, P=0.94). Patients and controls with normal initial encoding and good accuracy in the 10 sec condition also did not differ in accuracy (Z=0.0, p=1.0).

Discussion

This study examined the role of perceptual encoding on performance during an object WM task involving three delay intervals: a perceptual encoding condition (200ms) and two WM delay conditions (3 sec and 10 sec). Schizophrenia patients were significantly less accurate than controls on all three conditions. However, when the effects of perceptual encoding were separated from the effects of memory and retrieval, patients did not differ significantly from NC in the 3 sec condition. This result suggests that the worse mean performance of patients on the 3 sec delay interval was largely determined by poor initial encoding. In contrast, among patients who performed poorly at 10 sec, accuracy was equivalently reduced independent of encoding ability.

Impaired Perceptual Encoding or Impaired WM?

The distribution of accuracy scores in both groups (table 2) was not consistent with the uniform ceiling effects reported in previous studies that used 0-delay conditions. Indeed, substantial subgroups of patients (47%) and NC (22%) had difficulty with perceptual encoding. However, impaired initial perceptual encoding accounted for poor performance in the 3 sec delay only in patients. Poor encoding patients performed significantly worse in the 3 sec delay condition than good encoders with impaired accuracy on the 3 sec delay. These individual differences in perceptual encoding ability in patients are consistent with the well-documented heterogeneity of performance on cognitive measures in SZ patients (Heinrichs, 2004). In particular, previous studies have shown selective deficits in verbal, but not nonverbal, WM in subgroups of patients who performed normally on screening tests of attention and perception (Wexler et al., 1998, Bruder et al., 2004, Bruder et al., 2011). In contrast, patients who performed abnormally on the screening tests of attention and perception showed more generalized WM and cognitive deficits. Importantly, between-group comparisons of patients and NC that do not take into account heterogeneity in perceptual encoding ability result in two related inaccuracies: underestimating the magnitude of the encoding deficit in the subgroup with impaired encoding and overestimating it in the group as a whole (Buchsbaum and Rieder, 1979, Coleman et al., 2010).

The present study confirms prior findings implicating impaired initial perceptual encoding as the basis for what has been interpreted as WM deficits as well as substantial within-group variability in perceptual encoding in schizophrenia patients. Indeed, one DMTS object WM study showed that patients needed an approximately fivefold increase in stimulus duration relative to control subjects in order to effectively encode stimuli into WM [M(SD) = 2163(457) versus 421(473) msec, respectively].(Hartman et al., 2003) The relatively short stimulus duration (250 msec) used in the present study may have been too short for the subgroups of patients and NC who were poor encoders. An alternative design would extend

stimulus exposure times to determine whether longer stimulus durations normalize performance in these groups. Nevertheless, our results and those of others (Hartman et al., 2003, Neufeld, 2007, Badcock et al., 2008) implicate speed of visual perceptual encoding in the encoding deficit we observed in a subgroup of schizophrenia patients. Our results are also consistent with results from other cognitive tasks showing that increased latency of stimulus encoding is a key cognitive deficit of schizophrenia (Neufeld, 2007). Notably, the 250 msec stimulus duration was adequate for those subgroups of patients (53%) and NC (79%) who were able to encode at high levels of accuracy.

Slowed consolidation of WM has been reported in schizophrenia patients (Knight et al., 1985, Fuller et al., 2005, Vogel et al., 2006). We cannot rule out the possibility that a combination of deficits in speed of processing during initial encoding and slowed WM consolidation contributed to our findings. However, unless initial encoding takes place, WM consolidation cannot occur. Further, if slowed WM consolidation accounted for the findings, patients would have been expected to perform better on the 3 sec delay than on the 200 msec delay, but both groups did worse on the 3 sec delay. A backward masking effect from the probe also seems unlikely since our task involved a 250 msec exposure to perceive the stimulus before the probe was presented 200 msec later.

Perceptual Encoding and Early Visual Processing

Our finding implicating a perceptual encoding deficit is consistent with an extensive literature showing dysfunction in schizophrenia patients during the earliest stages of visual information processing (McGhie and Chapman, 1961, Miller et al., 1979, Saccuzzo and Braff, 1981, Green and Walker, 1986). Haenschel and colleagues carried out an object WM study using parallel event-related potentials (ERPs) and functional magnetic resonance imaging (fMRI) in early-onset schizophrenia. They linked impaired generation of event-related components (e.g., P1, P370) reflecting early stage visual processes to decreased blood oxygenation levels in extrastriate visual areas during encoding of abstract shapes (Haenschel et al., 2007). Specifically, patients showed reduced amplitude of various ERP components and decreased brain activation in highly overlapping areas of the visual cortex during both encoding and retrieval.

The visual cortex is organized into two major visual streams - object (what) information and spatial (where) information, which are processed in the ventral and dorsal visual streams, respectively (Merigan and Maunsell, 1993, Callaway, 1998). Ventral stream processing of object information has been linked to the lateral occipital cortex (LOC) by high-density electrical mapping (Doniger et al., 2000, Sehatpour et al., 2010) and fMRI (Malach et al., 1995, Green et al., 2009, Sehatpour et al., 2010) studies. Visual input from the ventral and dorsal visual streams, corresponding to the parvocellular and magnocellular visual systems, respectively, converges within the LOC. ERP studies of visual processing suggest that the initial stages of ventral stream processing are generally intact in schizophrenia patients whereas impaired magnocellular/dorsal stream functioning may be responsible for secondary downstream impairment within ventral stream object processing regions in the LOC (Doniger et al., 2002, Sehatpour et al., 2010, Dias et al., 2011, Martinez et al., 2011). Thus, the visual perceptual encoding deficit implicated in this study and others may reflect magnocellular dysfunction contributing to a secondary processing impairment within the ventral stream pathway and object processing regions in the LOC.

Relation between Initial Encoding and Length of Delay Interval

In the longer delay condition patients tended to perform less accurately than NC, even after encoding ability was taken into account. Notably, initial encoding ability cannot fully account for patient performance in this condition, suggesting that factors related to “on-line”

maintenance of a durable representation in WM played a greater role in impaired performance than did initial encoding. Our findings implicating impaired initial perceptual encoding in WM memory deficits at shorter delay intervals and deficits in maintaining an accurate representation within WM at longer intervals, are consistent with other work showing both abnormal encoding and WM maintenance deficits in schizophrenia (Tek et al., 2002, Glahn et al., 2003, Lencz et al., 2003). Taken together, these findings are consistent with recent evidence showing that early sensory and later cognitive ERP components contribute independently to impaired visual WM performance (Dias et al., 2011).

In summary, we showed that a distinct subgroup of schizophrenia patients with poor visual perceptual encoding accounted for worse object WM performance in patients than controls on a 3 sec delay condition. The visual encoding deficit implicates early visual processing, likely reflecting processes related to the speed of visual perceptual encoding in WM impairments in schizophrenia. Impaired accuracy in patients on the 10 sec delay was unrelated to initial perceptual encoding, thereby implicating WM maintenance deficits. Our findings indicate that object WM deficits in some patients, at least at shorter delay intervals, are largely a function of poor initial perceptual encoding. Our results also suggest a disproportionately greater role for processes related to maintenance and retrieval in object WM deficits observed at longer delay intervals. Although behavioral results cannot be conclusively linked to specific neurophysiological processes, our results are consistent with other data implicating dysfunction of both bottom-up sensory processing brain regions in the visual cortex as well as in top-down higher cortical storage areas involved in the active maintenance of information during longer delay intervals (Tek et al., 2002, Lencz et al., 2003, Dias et al., 2011).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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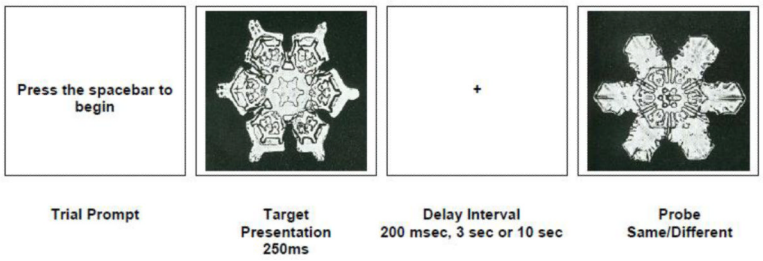

Figure 1.
Snowflake Object Working Memory Task

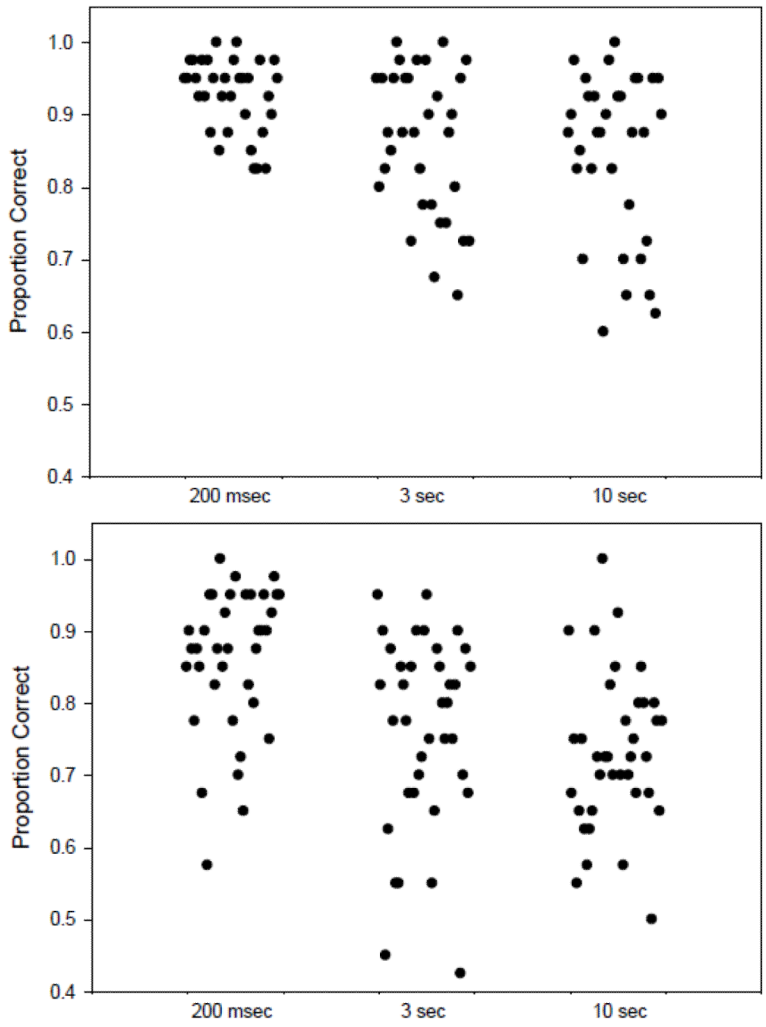

Figure 2.

a. Distribution of Accuracy Scores in NC Subjects for the Delay Intervals

b. Distribution of Accuracy Scores in Schizophrenia Patients for the Three Delay Intervals

Table 1

Demographic Characteristics of the Study Sample

Group	N	Age (yrs)	Gender (% male)	Estimated Verbal IQ*	Years of Education	SES
SZ	37	39.8 (9.2) [26.8–52.0]	60	99.2 (10.6) [85–120]	13.9 (2.0) [12–18]	2.7 (1.2) [1-5]
NC	33	40.3 (12.4) [18.8-60.4]	36	107.7 (9.6) [95-130]	15.0 (2.9) [11-21]	2.6 (1.1) [1-5]

Mean (SD) [range]

Schizophrenia patients had significantly lower mean estimated verbal IQ (t=3.3, df=6, P=0.001) and tended to be disproportionately male compared with the NC group (χ^2=3.6, df=1, P=0.06). Estimated verbal IQ data available on 28/33 controls.

Table 2

Mean Accuracy Scores (and Standard Deviations) for the Three Delay Intervals

Group/Delay	N	200 ms	3 sec	10 sec
Schizophrenia	37	0.86 (0.10) *	0.76 (0.13) **, †	0.73 (0.11) ***, ††
Controls	33	0.93 (0.05)	0.86 (0.10) ‡	0.85 (0.11) ‡‡

Between group differences:

Schizophrenia patient within group differences:

NC within group differences:

* P<0.003 (Z=2.97, es-1.27);

** P<0.002 (Z=3.18, es=1.0);

*** P<0.0002 (Z=3.77, es=1.0).

† P<.0.0001(S=248.0, es=0.83);

†† P<0.0001(S=285.5, es=1.17).

‡ p<0.002(S=140.0, es=0.68);

‡‡ P<0.0001(S=182.5, es=0.77).

Table 3

Mean (SD) Accuracy for the 3 and 10 sec Delay Intervals in Individuals with Poor Accuracy[1] at 3 seconds and in Individuals with Poor Accuracy[1] at 10 seconds: Subgroups Stratified on the Basis of Good[2] versus Poor[1] Initial Encoding

	Subgroups (%)	Accuracy: 3 Second Delay	Accuracy: 10 Second Delay
NC[3,4]	Poor Encoders	0.79 (0.08), n=7	0.70 (0.08), n=5 [+]
	Good Encoders	0.79 (0.07), n=11	0.79 (0.09), n=13 [+]
SZ[3,4]	Poor Encoders	0.68 (0.13), n=16	0.70 (0.09), n=18 [*]
	Good Encoders	0.79 (0.09), n=15	0.72 (0.07), n=15 [*]

[+] P=0.08

[*] P=0.02

[1] Poor accuracy at 3 seconds or 10 seconds denotes the proportion of correct responses below 0.90 (<90% correct).

[2] Good accuracy at 3 seconds or 10 seconds denotes the proportion of correct responses on or above 0.90 (≥90% correct).

[3] All poor encoders had poor accuracy on both the 3 and 10 second delay conditions.

[4] The average accuracy values for good encoders on the 3 and 10 second delay conditions were equivalent in the two groups (3 seconds - NC: 0.95 (0.03), n=14; SZ: 0.92 (0.03), n=3; 10 seconds - NC: 0.94 (0.03), n=12; SZ: 0.94 (0.05), n=3)