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Verbal memory in schizophrenia: additional evidence of subtypes having different cognitive deficits

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Abstract

A prior study found a selective deficit in verbal working memory in a subgroup of patients with schizophrenia who performed as well as healthy controls on a screening test of attention and auditory perception [Arch. Gen. Psychiatry 55 (1998) 1093]. Given the importance of defining pathophysiologically distinct subtypes of schizophrenia, the present study aimed to replicate and extend this finding. Patients with schizophrenia who passed the screening test (discriminators or Dsz patients) were compared to those who did not (nondiscriminators, NDsz patients), and healthy controls on a word serial position test (WSPT) and on other tests of verbal and nonverbal cognitive function. Dsz patients performed more poorly than controls on the WSPT and showed serial position effects consistent with a verbal memory deficit. They also showed a deficit in verbal memory but not visual memory on the Wechsler Memory Scale-Revised. In contrast, the NDsz patients showed overall poor performance on both verbal and nonverbal tests, consistent with a generalized deficit. Verbal working memory deficits were not related to education, gender, severity of symptoms, medication status, or hemispheric dominance for perceiving dichotic words. The findings add to growing evidence for the existence of a subgroup of schizophrenia having a specific verbal memory deficit that is not limited to working memory, but extends to learning and recall of verbal material.

Keywords: Working memory; Schizophrenia; Cognitive subtypes; Negative symptoms

1. Introduction

Studies using visually presented spatial or verbal stimuli have found evidence that working memory impairment is a primary cognitive deficit in schizophrenia (Park and Holzman, 1992; Carter et al., 1998; Cohen et al., 1997; Perlstein et al., 2001; Callicott et al., 2000). Patients with schizophrenia also show deficits in verbal working memory on auditory tasks (Gold et al., 1997; Wexler et al., 1998; Menon et al., 2001). Gold et al. used a letter–number sequencing task, in which subjects must simultaneously store and manipulate the order of spoken letters and numbers. Patients showed deficits on this task, which were

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highly correlated with performance on the Wisconsin Card Sorting Test. They suggested that impairments of working memory may be responsible for some of the generalized deficits found in schizophrenia on multiple cognitive tests. However, this also raises an important question that has plagued neuropsychological studies of schizophrenia. How does one differentiate between a generalized deficit in cognitive function and a deficit that is specific to the cognitive function under study, e.g., verbal working memory? Similarly, to what extent does the poor performance of patients on working memory tests reflect a generalized deficit due to reduced attention or motivation?

Wexler et al. (1998) found evidence of a selective deficit of verbal working memory in a subgroup of patients with schizophrenia who were tested on an auditory word serial position test (WSPT). This working memory test requires storage and rehearsal of phonological and sequential information over a delay of up to 9 s. Before patients were tested on the word and a tone serial position test, they were divided into two subgroups based on their ability to perform normally on a tone discrimination test requiring sustained attention and auditory perception. Wexler et al. reasoned that to study verbal working memory in schizophrenia it would be important to first determine whether or not the patients could adequately attend to and perceive auditory stimuli. Patients who performed as well as healthy controls on the tone discrimination test also showed normal performance on the tone serial position test, but showed deficits on the WSPT. The fact that this subgroup performed as well as controls on a tone discrimination task and working memory test that for controls was more difficult than the WSPT argues against their poorer verbal memory being due to a generalized deficit. In contrast, patients who performed poorly on the tone discrimination test had marked deficits on *both* the word and tone serial position tests, which is suggestive of a generalized deficit perhaps due to reduced attention, perception or motivation.

The present study extends this earlier work and provides further evidence for the existence of schizophrenia subtypes having either a verbal memory deficit or a generalized cognitive deficit. As in the Wexler et al. (1998) study, a tonal discrimination test was used to identify a subgroup who performed as well as controls on a test of attention and auditory perception (i.e., discriminators or Dsz patients) and a subgroup who performed poorly on this screening test (i.e., non-discriminators or NDsz patients). Use of the WSPT, which requires subjects to remember the order of four spoken words, also permitted an examination of accuracy as a function of the serial position of words in the sequence. Elvevåg et al. (2002) tested patients with schizophrenia on a probed letter recall task, in which participants read a list of letters aloud and then were required to name the letter that occurred in a specific serial position. They reasoned that if poor performance in patients were due to general deficits in motivation or attention, one would expect greater errors distributed fairly equally across serial positions. They did not find this to be the case, but rather found the patients had poorer performance than controls at the list's beginning and middle, items that had to be held in memory the longest. In the present study, it was hypothesized that Dsz patients with verbal memory impairment would show greater deficit for words presented at earlier serial positions because they must be held in memory longer. In contrast, the NDsz patients having a generalized deficit would perform markedly poorer than controls regardless of the serial position of the word.

Although visuospatial working memory deficits have been replicated in both medicated and unmedicated patients with schizophrenia (Carter et al., 1996; Park and Holzman, 1992; Park et al., 1999), the patients in the Wexler et al. (1998) study of verbal working memory were all receiving psychiatric medications. A secondary purpose of this study was therefore to compare the performance of medicated and unmedicated patients on the WSPT.

A further purpose was to compare the Dsz and NDsz subgroups on other tests of verbal and nonverbal cognitive function. Two questions were of particular interest. First, is the verbal memory deficit in Dsz patients specific to working memory or does it extend to learning and recall of verbal information, e.g., as measured by the Wechsler Memory Scale-Revised (WMS-R; Wechsler, 1987)? Second, would NDsz patients show overall poor performance on *both* verbal and nonverbal tests consistent with a generalized deficit in cognitive function, but Dsz patients show a more selective deficit in verbal memory?

Lastly, findings from neuroimaging studies have revealed material-specific laterality effects, with main-

tenance of verbal information preferentially activating left inferior frontal, parietal, and temporal regions (Barch et al., 2002; Kelly et al., 2002; Prabhakaran et al., 2000; Smith and Jonides, 1999). Theories concerning disturbances of cerebral lateralization in schizophrenia suggest the hypothesis that the verbal working memory deficit in Dsz patients may predominantly involve language-related processes in these left hemisphere regions. Most patients and controls in this study also received dichotic listening tests for assessing hemispheric asymmetry for perceiving words or complex tones. This allowed us to evaluate whether or not the verbal memory deficit in Dsz patients was accompanied by reduced left hemisphere dominance for perceiving words.

2. Methods

2.1. Participants

A total of 29 patients (17 male, 12 female) were recruited from New York State Psychiatric Institute. They were inpatients at the Schizophrenia Research Unit, with the exception of one patient who was attending an outpatient facility associated with this unit. The patients met DSM-IV (American Psychiatric Association, 1994) criteria for schizophrenia ($n=23$) or schizoaffective disorder (bipolar type, $n=2$; depressive type, $n=4$). Research consensus diagnoses were based on clinical interviews and a semistructured interview by a trained and reliable rater using the Diagnostic Interview for Genetic Studies (Nurnberger et al., 1994), which included items from other commonly used instruments (e.g., Structured Clinical Interview for DSM-III-R, patient edition, Spitzer et al., 1990; Scale for the Assessment of Negative Symptoms and Scale for the Assessment of Positive Symptoms, Andreasen, 1983, 1984). Symptom ratings were also obtained using the Positive and Negative Syndrome Scale (PANSS; Kay et al., 1992). A total Brief Psychiatric Rating Scale (BPRS) score was derived from the 18 PANSS items that match those in the BPRS. Patients were tested on the average 59 days after admission (range = 5 to 227 days). When tested, 17 patients were receiving antipsychotic medications, which were risperidone ($n=7$), clozapine ($n=5$), or olanzapine ($n=5$). The remaining 12 patients did not receive antipsychotic medications for at least 14 days before testing.

A control group consisted of 26 healthy adults (14 male, 12 female) who were recruited from the New York metropolitan area and paid $15 per hour for participation. Controls were interviewed using the Structured Clinical Interview for DSM-IV, nonpatient edition (First et al., 1996) to exclude those with current or past psychopathology. Both controls and patients were excluded from the study if they had a hearing loss greater than 30 dB in either ear at 500, 1000 or 2000 Hz or if they had a history of neurologic insult or illness, or current or past episodes of substance abuse. After a description of the study to participants, written informed consent was obtained before initiating tests.

2.2. Tone discrimination screening test and classification of Dsz and NDsz patients

In a tone discrimination test of attentional and perceptual competence, participants judged whether two 200 ms pure tones separated by a 100 ms interval were the same or different in pitch. When the tones were different, the frequency ratios were 0.67, 0.75, 0.85, 0.90 or 0.95. The tone frequencies ranged from 325 to 1994 Hz. There were 10 practice trials and 60 test trials—30 test trials where the tones were the same pitch and 30 trials where the tones were different, with each of the five frequency ratios occurring once in each block of 10 trials. Trial types were randomly distributed within the block.

Patients were separated into discriminators (Dsz, $n=17$) or nondiscriminators (NDsz, $n=12$) on the basis of scores on the tone discrimination test. Patients were considered to be Dsz if they were 100% correct, or at most made one error in 12 trials, at the two easiest pitch discrimination ratios (0.67 and 0.75). The remainder of the patients who did not pass this screening criterion were considered to be NDsz. All controls met this screening criterion.

2.3. Word serial position test (WSPT)

In the WSPT (Wexler et al., 1998), each trial begins with four nouns spoken in a male voice with 1 s between words. One of these words was then repeated after a delay of 9 s. Participants were instructed to remember the four words in the order presented and to

indicate the position of repeated word by pointing to response cards labeled 1 through 4. There were 36 trials, randomly ordered and balanced with regard to the four serial positions. No word appeared twice in the test.

2.4. Dichotic listening tests

To assess left hemispheric dominance for perceiving words and right hemisphere dominance for perceiving complex tones, 22 of the patients (15 Dsz and 7 NDsz) and all controls completed two dichotic listening tests. The Fused Rhymed Words Test (Wexler and Halwes, 1983) consists of 15 different word pairs in which members of every pair differ only in the initial consonant, e.g., bear, tear. All words begin with one of six stop consonants (b, d, p, t, g, k) recorded in a synthesized male voice. When presented dichotically, the two words fuse into a single audio percept. Participants indicated the word they heard by marking an answer sheet that had four possible responses, both members of the dichotic pair and two foils. Following practice trials, each participant received four 30 item blocks for a total of 120 trials. Orientation of headphones was reversed after the first and third blocks. The stimuli were presented via matched TDH-49 headphones at a comfortable level of 75 dB sound pressure level (SPL). The Complex Tone Test (Sidtis, 1981) requires participants to compare the pitch of a binaural complex tone to the pitches of a dichotic pair presented 1 s earlier. Participants pointed to a response card labeled YES when the probe tone was the same as either member of the previous dichotic pair, or to a card labeled NO when the probe tone differed from both. The complex tones were square waves with fundamental frequencies corresponding to the eight notes in the octave between C4 and C5. After practice trials, participants were tested in four blocks of 28 trials in which half of the probe tones matched a member of the dichotic pair and half did not. Orientation of headphones was again reversed after the first and third blocks.

2.5. Neuropsychological tests

Twenty-two of the patients (Dsz = 13, NDsz = 9) were also tested with the WAIS-III and WMS-R as part of other research at the Schizophrenia Research Unit. This made it possible to compare the Dsz and NDsz patients on verbal and performance IQ and on WMS-R indexes of verbal and visual memory.

2.6. Statistical analyses

Comparison of demographic variables between the Dsz, NDsz and control groups were performed using a one-way ANOVA followed by Newman–Keuls post-hoc tests to contrast groups, and differences between the Dsz and NDsz on clinical and neuropsychological tests were evaluated using independent *t*-tests. The percentage of correct responses to pitch differences on the tone discrimination task were analyzed using a three (Group) by five (Ratio of Tones) repeated measures ANOVA. Accuracy scores on the WSPT were submitted to a three (Group) by four (Serial Position) repeated measures ANOVA. On the dichotic listening tests, the number of correct responses for items presented to the right (R) and left (L) ears were used to compute a perceptual asymmetry score for the word and tone tests, i.e., $100(R-L)/(R+L)$. The asymmetry scores for the Dsz, NDsz and control groups on each test were submitted to a one-way ANOVA. A two (Group) by two (Ear) ANOVA was also performed on the absolute accuracy scores for the Complex Tone Test. This analysis was not performed on the data for the words test because accuracy was essentially 100% correct for the single response given on each trial.

3. Results

3.1. Demographic and clinical variables

Table 1 gives the demographic variables for the three groups. There was no significant difference among groups in age, but there were fewer females in the NDsz group. The potential impact of gender on group differences in WSPT performance is therefore examined below. The NDsz group also had significantly less education than the Dsz or control groups ($F = 10.55$, $df = 2,52$, $P < 0.001$). Performance on the WSPT was not, however, significantly correlated with education level in either patients or controls, and entering education as a covariate did not alter the significance of group differences in WSPT perfor-

Table 1
Demographic and clinical variables

Variable	Discriminators ($n=17$, 8 Male)		Nondiscriminators ($n=12$, 9 Male)		Controls ($n=26$, 14 Male)	
	Mean	S.D.	Mean	S.D.	Mean	S.D.
Age (years)	32.7	9.4	28.1	7.5	28.0	7.0
Education (years)	14.5	1.9	12.4[a]	2.3	15.5	1.7
Handedness (LQ)	59.6	49.9	56.0	59.0	61.8	51.6
Onset age (years)	23.6	8.0	22.0[b]	4.6		
Illness duration (years)	9.5	10.4	6.0[b]	7.2		
Total BPRS	28.8[c]	4.5	30.0[d]	5.4		
PANSS positive	12.9[c]	4.2	11.3[d]	4.5		
PANSS negative	11.8[c]	4.3	17.2[d,e]	6.5		

LQ, laterality quotient (range −100 to 100); BPRS, Brief Psychiatric Rating Scale; PANSS, Positive and Negative Syndrome Scale.

[a] Nondiscriminators differ significantly from discriminators and healthy controls ($P<0.05$).

[b] $n=11$.

[c] $n=16$.

[d] $n=10$.

[e] Nondiscriminators differ significantly from discriminators ($P<0.05$).

mance. The Dsz and control groups did not differ in gender or education. There was no difference among groups in handedness laterality quotient (LQ) on the Edinburgh Handedness Inventory (Oldfield, 1971), where a LQ of 100 signifies complete right-hand preference and −100 indicates complete left-hand preference. The Dsz and NDsz patients did not differ in age of onset or illness duration. An equal percentage of Dsz patients (41.2%) and NDsz patients (41.7%) were off medication when tested and the remainder of patients in each group were receiving atypical antipsychotics. Although there was no difference between the patient groups in overall severity, as indexed by total BPRS scores for 16 Dsz and 10 NDsz patients, or in their positive symptoms on the PANSS, the NDsz patients did have significantly greater negative symptoms than the Dsz patients ($t=2.57$, $df=24$, $P<0.05$). Greater negative symptoms was associated with poorer tone discrimination on the screening test ($r=-0.64$, $p<0.001$), but its correlation with overall performance on the WSPT was not statistically significant ($r=-0.34$, ns).

3.2. Tone discrimination test

As shown in Fig. 1, there was no difference in tone discrimination between the Dsz and control groups not only at the two easiest pitch ratios (0.67 and 0.75), where they were close to 100% correct, but also at the most difficult ratios (0.90 and 0.95). In contrast, the NDsz patients performed considerably poorer than Dsz patients and controls at all pitch ratios. An ANOVA of these data revealed significant main effects of Group ($F=42.87$, $df=2,52$, $P<0.001$) and Pitch Ratio ($F=17.44$, $df=4,208$, $P<0.001$), but no interaction between these variables. ANOVA comparing each pair of groups and retaining pitch ratio as a second factor indicated that the overall percentage of correct tone discriminations in NDsz patients was significantly less than either Dsz patients or controls ($P<0.001$), but there was no significant difference between the Dsz patients and controls.

3.3. WSPT

Fig. 2 shows the mean accuracy scores of the Dsz, NDsz, and control groups for each of the four serial positions on the WSPT. As can be seen, Dsz patients performed as well as controls for words in the 4th position, but showed poorer accuracy for words presented earlier in the sequence. In contrast, NDsz patients performed worse than both the Dsz patients and controls at all serial positions. An ANOVA of these

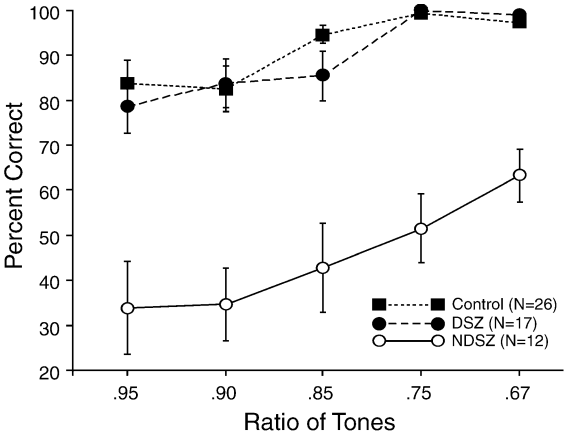

Fig. 1. Mean percentage of correct discriminations for each group as a function of frequency ratio of the tone pairs in the screening test (error bars = standard errors of the mean).

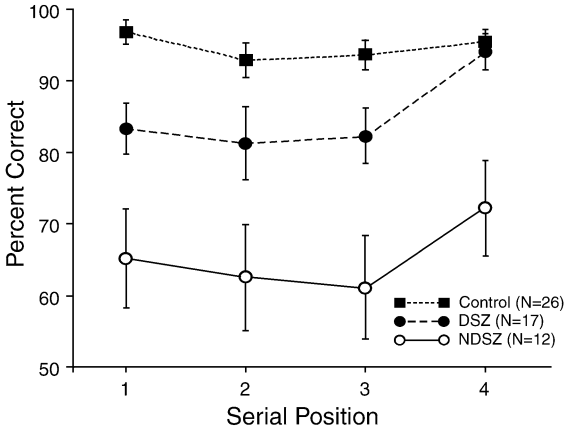

Fig. 2. Mean percentage of correct responses for each group as a function of the serial position of words in the WSPT (error bars = standard errors of the mean).

data revealed significant main effects of Group (F = 31.34, df = 2,52, P < 0.001) and Serial Position (F = 4.06, df = 3,156, P < 0.01). A separate ANOVA of accuracy scores for each serial position indicated that the differences among groups were significant at all positions (F=10.8, df = 2,52, P < 0.001). Newman–Keuls post-hoc tests revealed that NDsz patients had poorer accuracy than Dsz patients and controls for words at all serial positions (P < 0.05). Dsz patients had significantly poorer accuracy than controls for words in the 1st serial position (P < 0.05) and a trend toward poorer accuracy in the 2nd and 3rd positions (P < 0.10), but not in the 4th position. Thus, the Dsz patients showed an intact recency effect but impaired primacy effect.

To further examine the selective nature of the impairments in Dsz and NDsz subgroups, an ANOVA was performed in which accuracy scores on the WSPT and tone discrimination test were treated as a repeated measures factor and the three groups as a between subjects factor. There was a Test by Group interaction (F = 8.95, df = 2,52, P < 0.001). Although a separate ANOVA for the tone test and the WSPT revealed a significant group difference for each test (P < 0.001), the differences among groups varied markedly across these tests. Post-hoc multiple comparisons indicated that the NDsz patients (M = 45.2, S.D. = 23.4) had significantly poorer accuracy than either Dsz patients (M = 89.4, S.D. = 11.8) or controls (M = 91.6, S.D. = 11.9) on the tone discrimination test (P < 0.05), but there was no difference between the Dsz patients and controls on this test. On the WSPT, both the NDsz patients (M = 65.2, S.D. = 18.6) and Dsz patients (M = 85.3, S.D. = 8.7) had significantly poorer accuracy than controls (M = 94.7, S.D. = 6.0, P < 0.05), and the difference in accuracy between the Dsz and NDsz groups was considerably less than seen for the tone test.

Given the smaller number of females in the NDsz group than the other groups, two additional analyses were performed to examine the potential contribution of gender. First, the ANOVA of the WSPT data was repeated comparing only the men in the three groups. The differences in WSPT accuracy remained essentially the same as seen for the full samples, with significant main effects of Group (F = 17.02, df = 2,28, P < 0.001) and Serial Position (F = 2.80, df = 3, 84, P < 0.05). Male controls had the highest accuracy (M = 95.8, S.D. = 3.3), followed by male Dsz patients (M = 87.5, S.D. = 10.0) and male NDsz patients (M = 71.3, S.D. = 15.4). Second, there were sufficient men and women in the Dsz and control groups (see Table 1) to perform an ANOVA of their WSPT accuracy scores using gender as an additional grouping variable. There was a significant difference in accuracy between the Dsz and control groups (F = 16.94, df = 1,39, P < 0.001), but no gender effect or group by gender interaction.

The potential influence of antipsychotic medication on working memory was examined by comparing the WSPT performance of 17 patients receiving atypical antipsychotics and 12 unmedicated patients. These groups did not differ significantly in age, education or handedness. A two (Group) by four (Serial Position) ANOVA revealed a significant main effect of Serial Position (F = 3.52, df = 3, 81, P < 0.05), but there was no significant difference in accuracy between the medicated patients (M = 74.7, S.D. = 15.8) and unmedicated patients (M = 80.2, S.D. = 18.2). Both groups did perform significantly poorer than the controls (P < 0.05).

3.4. Dichotic listening tests

All three groups showed the expected right ear advantage on the dichotic word test, which reflects left hemisphere dominance for perceiving words. The mean right ear advantage for the Dsz patients (M = 12.0, S.D. = 15.2) was slightly smaller than for the NDsz patients (M = 15.8, S.D. = 9.7) and controls

(M = 15.5, S.D. = 20.8), but this difference was not statistically significant. The groups also showed the expected left ear advantage indicative of right hemisphere dominance for perceiving complex tones. There was no significant difference in the left ear advantage for complex tones for the Dsz patients (M = – 4.4, S.D. = 11.5), NDsz patients (M = – 10.4, S.D. = 5.6), and controls (M = – 7.1, S.D. = 9.5).

An ANOVA of the absolute accuracy scores for each group on the Complex Tone Test revealed a significant main effect of Group ($F = 3.70$, $df = 2,45$, $P < 0.05$) and Ear ($F = 22.89$, $df = 1,45$, $P < 0.001$), but no Group by Ear interaction. Post-hoc tests indicated that accuracy for perceiving complex tones was poorer in NDsz patients (M = 74.5, S.D. = 6.7) when compared to controls (M = 86.0, S.D. = 9.4; $P < 0.05$), whereas the Dsz patients (M = 80.6, SD = 13.4) had an intermediate accuracy level that did not differ significantly from either group.

3.5. Neuropsychological tests

NDsz patients showed generally poorer performance than the Dsz patients on the WAIS-IQ and WMS-R tests (see Table 2). They had lower verbal and performance IQ scores when compared to the Dsz patients. On the WMS-R, NDsz patients had significantly lower scores than Dsz patients on the visual memory index, but *not* on the verbal memory index. The Dsz patients performed as poorly as NDsz patients on the verbal memory index and had significantly lower scores on the verbal than the visual memory index ($t = 3.80$, $df = 12$, $P < 0.01$). In contrast, the NDsz patients did not show a significant difference between verbal and visual memory ($t = 0.97$, $df = 8$, ns).

Table 2
Neuropsychological measures of verbal and nonverbal functions

	Discriminators (Dsz) ($n = 13$)		Nondiscriminators (NDsz) ($n = 9$)		t	P
	Mean	S.D.	Mean	S.D.		
WAIS-III						
Verbal IQ	98.8	8.4	88.4	11.2	2.47	0.02
Performance IQ	88.4	7.7	72.7	11.2	3.91	0.001
Wechsler Memory						
Verbal memory	81.7	20.2	73.2	11.4	1.25	ns
Visual memory	103.5	22.3	81.9	22.0	2.25	0.04

The WMS-R indexes were standardized to have a mean of 100 and an S.D. of 15. The NDsz patients showed deficits on both the verbal and visual memory indexes, which were between 1 and 2 S.D.s below the mean for a standardization sample having about the same education, i.e., 12 years (Wechsler, 1987). The Dsz patients, with a mean education level of 14 years, were compared to a standardization sample with an education level greater than 12 years. The verbal memory score of the Dsz patients was between 1 and 2 S.D.s below the mean for this standardization sample (M = 107.6, S.D. = 14.7), but their visual memory score was essentially the same as the standardization sample (M = 105.5, S.D. = 13.4). Thus, the Dsz patients showed a verbal memory deficit but no visual memory deficit on the WMS-R, whereas the NDsz patients showed deficits in both verbal and visual memory.

4. Discussion

Patients with schizophrenia who performed as well as healthy controls on a screening test of attention and auditory perception, i.e., Dsz patients, displayed poorer verbal working memory on the WSPT, which replicates the findings of Wexler et al. (1998). These patients showed normal performance on the screening test even at the most difficult levels of pitch discrimination, where accuracy was equal to or less than on the WSPT. This indicates that their poorer verbal working memory than controls was not a byproduct of greater difficulty of the WSPT. The serial position effects for the Dsz patients were also consistent with a verbal memory deficit, in that they showed greater deficit for words presented in the beginning and middle of the sequence that must be held longer in memory. Their normal performance for words presented in the 4th serial position and for the tonal discrimination test makes it unlikely that their poorer memory for words presented earlier in the sequence was due to a generalized deficit. In contrast, patients who failed the auditory screening test, i.e., NDsz patients, performed more poorly than controls at all serial positions, which is more consistent with a generalized deficit due to reduced attention or perception.

The results also indicate that the verbal memory deficit in Dsz patients extends to the learning and recall

of verbal information on the WMS-R. Dsz patients scored as low as NDsz patients on the verbal index of the WMS-R and significantly lower on the verbal than the visual memory index. They scored 1 to 2 S.D.s less than the mean for the standardization sample (Wechsler, 1987), which is consistent with a large effect size (Cohen, 1988), but did not differ from the standardization sample on the visual memory index. This supports the conclusion that the memory deficit in the Dsz subgroup is specific to processing of verbal information. On the other hand, the NDsz subgroup showed abnormally poor performance on both the verbal and visual memory indexes of the WMS-R, consistent with their generalized deficit.

The tests that comprise the verbal and visual memory indexes on the WMS-R are not matched in their psychometric properties, which raises the possibility that the apparent differential deficit observed in Dsz patients on these sets of tests may be secondary to the psychometric differences (Chapman and Chapman, 1978). In two previous studies, however, Dsz patients had deficits on verbal but not nonverbal working memory tests, even though the nonverbal tests were more difficult for the healthy controls, i.e., Dsz patients had deficits on the easy test but not the harder test (Wexler et al., 1998, 2002). Thus, it seems likely that the deficit on verbal but not nonverbal tests in the Dsz patients is due to patient characteristics rather than psychometric differences between tests. Moreover, an advantage of using the tone discrimination task to divide patients into subgroups is that it yielded one group showing a pattern of results consistent with a generalized deficit, i.e., NDsz patients, whereas the other subgroup showed a deficit only on the verbal tests in this study, i.e., Dsz patients.

The WMS-R findings support the existence of a subgroup of schizophrenia having a verbal memory deficit that is not limited to working memory, but is also evident for verbal learning or recall over more extended periods. Barch et al. (2002) have argued that poorer performance of patients with schizophrenia on tasks assessing working memory and long-term memory may reflect a common disturbance in prefrontal cortex and perhaps medial temporal regions. In a functional magnetic resonance imaging (fMRI) study, they found that patients with schizophrenia failed to show evidence of greater activation for words than faces in regions that typically demonstrate material-specific activation in healthy adults, i.e., left inferior prefrontal cortex, left parietal cortex and left temporal cortex. Similarly, Stevens et al. (1998) found that healthy adults showed greater activation of the left inferior frontal cortex during the WSPT than a tone serial position test. Patients with schizophrenia who had normal tone discrimination (i.e., Dsz patients) failed to show this task-specific activation during the WSPT, which suggests that this subgroup may have a dysfunction of verbal memory processes involving left inferior frontal cortex.

While the Dsz patients showed a deficit in verbal memory, their verbal IQ was in the normal range. This suggests that their poorer verbal memory on the WSPT and WMS-R was not due to a general impairment in verbal processing. On the other hand, their performance IQ was somewhat lower than might be expected for individuals with intact nonverbal abilities. It is possible that the Dsz patients may have impairments of cognitive abilities not assessed by the memory tests in this study. Further study is needed to determine the specific components of cognitive processing that are abnormal in Dsz patients.

There have been several reports of deficits in visuospatial working memory in schizophrenia (e.g., Carter et al., 1996; Park and Holzman, 1992; Park et al., 1999). None of these studies first screened patients for basic attentional or perceptual competence, which makes it impossible to compare their results to those in the present study. If all our patients had simply been combined into one group, we would have found deficits on both the verbal and nonverbal tests. It was only after first identifying patients who had preserved attentional and perceptual competence that we discovered evidence of deficit specificity. It is likely that the NDsz patients would show deficits on tests of visuospatial memory. We do not, however, think it is meaningful to assess memory function (verbal or spatial) without first screening patients for attentional and perceptual competence.

Despite their verbal memory deficits, Dsz patients did *not* differ significantly from healthy controls in their perceptual asymmetry for dichotically presented words. This is consistent with evidence that the verbal memory deficit in Dsz patients does not involve an abnormality in an early, perceptual stage of processing. Wexler et al. (2002) used serial position tasks designed to bypass perceptual processing of verbal material, in

which familiar sounds or line drawings were presented and participants were required to remember the word associated with these stimuli. Dsz patients continued to show working memory deficits in these tasks providing clear evidence that their verbal memory deficit was independent of sensory processing of verbal input. Given the primary involvement of temporal lobe regions in perceptual asymmetries for dichotic listening tests (Hugdahl, 1995), the normal dichotic listening in Dsz patients suggests that their verbal memory deficit does not stem from dysfunction in these temporal lobe regions, but rather left inferior frontal regions involved in generating or maintaining language-based representations (Stevens et al., 1998).

Although studies have found reduced left hemisphere advantage for perceiving dichotic fused words in schizophrenia (Bruder et al., 1995; Wexler et al., 1991), this is not a universal finding (e.g., Wale and Carr, 1988). Reduced left hemisphere advantage for words appears to be most evident among patients with greater positive symptoms, in particular hallucinations (Bruder et al., 1995; Green et al., 1994) and in patients with nonparanoid schizophrenia (Friedman et al., 2001). Although reduced left hemisphere advantage may be present in a subtype of schizophrenia, it was not evident in either the Dsz or NDsz subgroups. This could be a function of their specific clinical features or the low statistical power of these relatively small samples.

One question is whether differences in clinical features or other characteristics between Dsz and NDsz patients might account for their difference in verbal memory. Although there were fewer females in the NDsz subgroup, there was no evidence of gender effects on the WSPT, which is consistent with prior findings (Wexler et al., 2002). The NDsz patients also had somewhat less education than the Dsz patients, but education level was not related to performance on the WSPT, and group differences on this test remained when education was a covariate. The Dsz and NDsz subgroups did not differ in overall severity of symptoms (as indexed by total BPRS scores), age of onset or duration of illness. The NDsz patients did, however, have greater negative symptoms on the PANSS when compared to the Dsz patients. Greater negative symptoms was associated with poorer performance on the screening test of attention and auditory perception, but was not significantly related to verbal working memory. It is therefore possible that the general deficits observed in NDsz patients are in part related to reduced attention or perception and associated negative symptoms. Further study should be given to clinical features in Dsz patients that might be associated with their specific verbal memory deficits. For instance, Nestor et al. (1998) found that severity of thought disorder, as measured by the Thought Disorder Index, was associated with poor performance on neuropsychological tests of verbal memory, but not visual memory.

Questions may also be raised as to whether the medication status of the patients was a critical factor. In a global sense, this is unlikely because studies have found abnormal visuospatial working memory in both medicated and unmedicated patients with schizophrenia (Carter et al., 1996; Park and Holzman, 1992; Park et al., 1999), and in never-medicated relatives of patients (Cannon et al., 1994; Park et al., 1995). In the present study, there was no difference in the verbal working memory of unmedicated patients and those receiving atypical antipsychotics. Studies have found that atypical antipsychotics result in improvements of attention, executive function, working memory and other cognitive functions, but the effects varied depending on the specific atypical antipsychotic used in the study, i.e., clozapine, risperidone or olanzapine (Green et al., 1997; Keefe et al., 1999; Meltzer and McGurk, 1999). The effects were also relatively small in comparison to the marked differences in verbal working memory between the Dsz patients, NDsz patients and healthy controls. Moreover, given the broad nature of the effects of atypical antipsychotics on cognitive function, it is unlikely that this could account for the specific deficits in verbal memory seen in the Dsz patients.

The findings of this study have important implications for addressing the heterogeneity of schizophrenia, which remains an obstacle to advancing understanding of the pathophysiology of this disorder. Some patients, e.g., NDsz patients, may have impairment of a fundamental process like attention that leads to widespread deficits in performance on cognitive tests, while others, e.g., Dsz patients, may have impairment of a specific aspect of verbal memory that leads to more selective performance deficits. Individual differences in verbal memory or other cognitive functions might therefore be of value in defining "cognitive subtypes" with more homogeneous pathophysiology (Egan et al., 2001;

Wexler et al., 1998). Performance on these cognitive tests could provide specific behavioral criteria for selecting subgroups of patients for further study to characterize their clinical, neurophysiologic, and genetic characteristics.

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