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Deficits in multiple systems of working memory in schizophrenia

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Abstract

Working memory, the ability to hold and manipulate information ‘on-line’ in a temporary memory store, is impaired in schizophrenia. This impairment may be characterized within the framework of two opposing theoretical models: (1) central executive as coordinator of component processes of working memory or (2) multiple independent systems of spatial and object memory. In order to test which of these models better explains the working memory deficit of schizophrenia, 14 schizophrenic patients and 12 age- and gender-matched control subjects performed tests of spatial memory (dot location), object memory (shapes, color dots) and a dual paradigm (dot location+shapes). If schizophrenia impairs the central executive, a group-by-task interaction would demonstrate excessively worse performance on the dual than single tasks in schizophrenics relative to controls; however, the absence of an interaction would be consistent with deficits in the multiple working memory systems. The schizophrenic group was significantly impaired on all measures, and both the schizophrenic and control performance was worse on the dual than the single tasks. Despite the schizophrenic group performance deficits on the single tasks, the extent of such deficit did not appear additive and contributive to the dual tasks. The lack of a group-by-task interaction provided no support for the central executive model of dysfunction. Rather, the results uphold the model of working memory deficits arising from compromise of multiple (here spatial and object), relatively independent systems, both of which are affected in schizophrenia. © 1997 Elsevier Science B.V.

Keywords: Central executive model; Multiple frontal pathways model; Working memory; Schizophrenia

1. Introduction

The constellation of cognitive deficits commonly associated with schizophrenia includes impairment in problem solving, abstract thinking, planning

and explicit memory (Saykin et al., 1991; Heaton et al., 1994; Braff, 1993; Kolb and Whishaw, 1983; Sullivan et al., 1994). These deficits form part of the psychiatric syndrome of schizophrenia and may contribute to psychotic thought disorder (Greene, 1996). Central to impairments in these cognitive functions may be a deficit in working memory, which refers to the ability to hold and manipulate information ‘on-line’ in a temporary

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memory store (Baddeley, 1992; Goldman-Rakic, 1991; Fuster, 1995). Working memory is 'active and relevant only for a brief segment of time, usually on the scale of seconds' (Goldman-Rakic et al., 1990), and is useful for cognitive manipulations needed while performing a mental arithmetic problem.

The precise organization of working memory is still debated. Baddeley (1992) argues that working memory relies on a central executive and two auxiliary components: the visuospatial scratchpad and the phonological loop. According to this position, the central executive is essential as a coordinator of the two components during two concurrent tasks. Contrarily, working memory may comprise multiple component processes (Gabrieli, 1995) and constitute independent pathways responsible for the different processes. Based on single cell recording studies in primates, Wilson et al. (1993) outlined two distinct memory systems, each subserved by different anatomical pathways. The spatial (Where) system involves the pathway connecting the posterior parietal cortex, arcuate sulcus, dorso-lateral cortex and principal sulcus. The object (What) system involves the pathway connecting the inferior temporal cortex and inferior convexity of the frontal lobes. The human homolog to the inferior convexity is likely the inferior dorsolateral prefrontal areas, which have been implicated in schizophrenia (Berman et al., 1988; Weinberger et al., 1992; Goldman-Rakic, 1991).

The possibility of independent Where and What pathways runs counter to a unitary characterization of a central executive of working memory and to the necessity of this central executive. Baddeley et al. (1991) argue that Alzheimer's patients are especially impaired when simultaneously performing spatial and verbal tasks because of a damaged central executive. Contrarily, Parkinson's patients indicate no malfunction of the central executive while performing dual verbal, visual or spatial working memory tasks concurrent with articulatory suppression (Fournet et al., 1996). Imaging studies suggest that the spatial and verbal components of working memory segregate to distinct and separate regions of the human prefrontal cortex. Positron emission tomography has revealed activation in the left supramarginal gyrus during a verbal memory task (Paulesu et al., 1993), while spatial

memory localized to the middle frontal gyrus as seen with fMRI (McCarthy et al., 1994, 1996). More specific to schizophrenia, Park and Holzman (1992) reported spatial (Where), but not verbal, working memory deficits in schizophrenic patients, suggesting the presence of multiple, dissociable components of working memory.

The present study examined schizophrenic patients and normal control subjects, and employed experimental paradigms involving spatial and object working memory that tested the two theoretical conceptualizations of working memory. The paradigm evaluated separately spatial and object working memory and the potential interaction of these working memory components during a dual task, which taxed both systems. If, compared with the controls, the schizophrenic group showed an impairment in the dual task that was relatively greater than impairments in the single tasks, then these components would be considered as controlled by a central processor. If, however, the schizophrenic deficit was not excessively greater in the dual than single task conditions relative to control performance, then the multiple working memory systems model would be supported.

2. Methods

2.1. Subjects

All subjects gave written informed consent to participate in this study.

2.1.1. Patients with schizophrenia

This group included 14 men with schizophrenia. These patients were recruited from the Stanford University Mental Health Clinical Research Center, housed at the Palo Alto VA Medical Center, where they were diagnosed by consensus of two research clinicians according to strict Diagnostic and Statistical Manual of Mental Disorders (American Psychiatric Association, 1980) (DSM-III; $n=3$) or DSM-IV (American Psychiatric Association, 1995) criteria ($n=11$), derived from the Structured Clinical Interview for Diagnosis (Spitzer et al., 1992). The 14 patients

represented four subtypes: 1, disorganized; 2, paranoid; 2, residual; and 9, undifferentiated. Of these 14 schizophrenic patients, 13 were out-patients and one was an in-patient at the time of testing. Only out-patients were paid for participation in this study.

Patients were excluded for head injury, and for history of neurological illness or trauma that could affect the central nervous system. Patients were also excluded for substance abuse at the time of the test. Past substance-use information was ascertained by consensus of two clinical researchers during structured interviews. Interview revealed that 13 patients had not used illicit substances for at least 3 months prior to testing, and one patient for at least 1 month. Seven patients had no history of substance abuse or dependence at any time during their life although six had used illicit substances, while seven patients had substance abuse or dependence at one time prior to testing: seven non-alcoholic drug abuse, one alcohol abuse, two non-alcoholic drug dependence, and two alcohol dependence.

All patients but one were treated pharmacologically at the time of testing. Psychiatric medications included thiothixene, valproic acid, fluphenazine, benztropine, lorazepam, clozapine, lithium, risperidone, perphenazine, trihexyphenidyl and sertaline. Most of these medications are believed to have weak anticholinergic blocking effects, except perphenazine ($n=2$) with moderate anticholinergic effects and benztropine ($n=1$), clozapine ($n=5$), trihexyphenidyl ($n=1$) with high anticholinergic

effects. Five patients were taking medications with low anticholinergic effects and eight patients with relatively high anticholinergic effects.

The age at onset of schizophrenic symptoms was (mean \pm SD) 24.4 ± 4.3 years (range 19–32) and the average disease duration was 19.4 ± 5.9 years (range 8–28). Symptom severity was determined using the Brief Psychiatric Rating Scale (BPRS), which is an 18-item questionnaire evaluating the patient's mental and physical health. This test was given within 1 week (1.1 ± 2.4 days) of the working memory tests. The BPRS total score was 33.9 ± 6.2 points (range = 24.5–42.5), with higher scores indicating greater symptom severity (Overall and Gorham, 1962).

2.1.2. Normal control subjects

This group comprised 12 age- and gender-matched volunteers recruited from the community and paid for their participation. All subjects received a thorough physical and psychiatric examination and clinical interview to determine health status. Subjects were excluded for history of neurological illness or trauma that could affect the central nervous system, as well as current or past major psychiatric illness. Subjects were also excluded if they met Research Diagnostic Criteria (Spitzer et al., 1975) for substance abuse in the past year or had, at any time, non-alcoholic drug or alcohol dependence.

2.1.3. Group demographics (Table 1)

Group differences were tested with unpaired *t*-tests. The two groups did not differ significantly

Table 1
Group demographics: means, standard deviations (in parentheses) and ranges

Group	Age (years)	Education (years)	NART IQ	Handedness score ^a	Socio-economic status
Control ($N=12$)	38.8 (8.2) 27–52	15.6 (2.6) 12–20	113.7 ^b (7.3) 99–124	29.5 ^b (14.5) 14–66	41.4 ^c (23.8) 11–77
Schizophrenic ($N=14$)	43.1 (7.2) 29–54	13.9 (1.6) 11–17	109.1 (9.1) 95–124	16.2 (3.4) 14–25	44.0 (11.9) 22–62

^aFourteen to 32 signified right-handedness and 50 to 70 left-handedness.

^bBased on 11 control subjects.

^cBased on nine control subjects.

in age ($t(24)=1.438$, $p=0.1634$). Although the control group had significantly more years of education than the schizophrenic group ($t(24)=2.082$, $p=0.0482$), the two groups did not differ significantly in scores on the National Adult Reading Test (NART; Nelson, 1982), which provides an estimate of premorbid intelligence ($t(23)=1.365$, $p=0.1854$). In addition, the groups did not differ significantly in parental/caregiver socio-economic status ($t(21)=0.344$, $p=0.7346$), which was determined from the education and occupation of the subject's primary caregiver during the subject's entire lifetime (Hollingshead, 1975); lower scores signified higher status. Although both groups showed a right-hand preference, handedness was significantly different between the schizophrenic and control groups ($t(23)=3.353$, $p=0.0028$), as measured by a quantitative test (Crovitz and Zener, 1962); all schizophrenic patients were right handed, whereas seven controls were right handed, three non-right handed, one left handed and one unknown handedness.

2.2. Procedure

2.2.1. Single tasks

2.2.1.1. Spatial (Fig. 1). The subject began the experiment by fixating on a cross presented in the center of the computer screen for 500 ms. Then, a sequence of two dots was presented, with each dot

exposed for 250 ms in one of eight possible locations arranged in an oval. Following stimulus presentation, the subject fixated on the center cross for 3 s, after which he was given a sheet of paper with all eight locations and was asked to number the two locations in the order previously shown. This task determined the level of spatial memory ability. The sequence length started with two dots and increased to a maximum length of seven dots. The subject received two trials of each stimulus length. If the subject failed the first trial of a given length, he was given a second trial. The test was stopped when the subject failed on both trials to recall a sequence of the same length. Inter-trial intervals were not controlled and the task was subject-paced.

2.2.1.2. Object (Fig. 2). In this section, we examined object memory over two conditions of increasing difficulty: color and shape.

In the *color* condition, the subject began by fixating on a cross in the center of the computer screen for 500 ms. Then, a series of two colored dots appeared over the center cross, each colored dot was exposed for 250 ms. The subject once again fixed the center cross for 3 s, after which a paper was presented with all eight possible colors arranged vertically (blue, yellow, red, green, turquoise, gray, pink, black). The subject was asked to number the two colored dots in the order previously seen. The series started with two colored dots, until a maximum of seven, and the test was

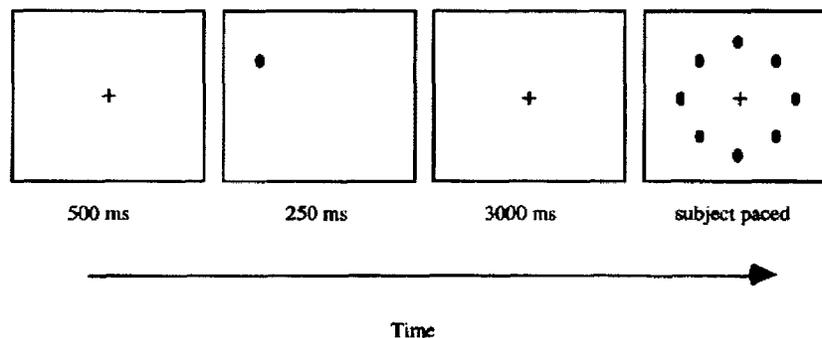


Fig. 1. Illustration of the order of events for each of the working memory tasks—shown here for the single spatial condition. The subject began by fixating on a cross in the center of the computer screen for 500 ms. A visual stimulus was then presented for 250 ms, following which the subject returned to fixating on the center cross for 3 s. The subject was then asked to recall the stimulus and the order on a separate paper. Activation of the next trial was subject paced.

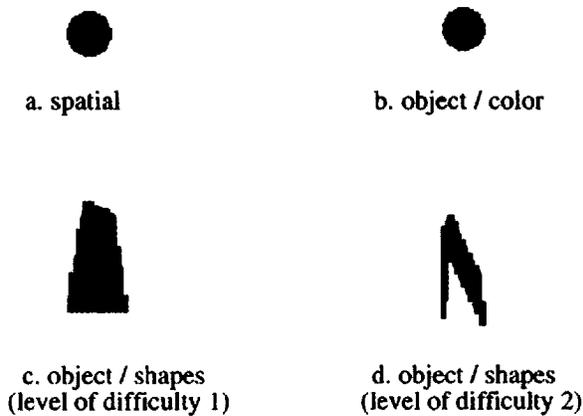


Fig. 2. Examples of the visual stimuli used in the working memory tasks: (a) single and dual spatial conditions, (b) single color condition, (c) and (d) single and dual shapes (Vanderplas figures) condition.

stopped once the subject failed both trials of one length of the colored dots series. Before starting the color condition, the subject performed a control task, which required him to match colors appearing on the computer screen with those on the paper and to name all eight colors. This pretest provided assurance that the subject had the required ability to discriminate and name all test stimuli.

The *shapes* stimuli followed the same presentation as the color condition, only now the subject's object memory was tested for solid black Vanderplas figures. These figures were created by connecting randomly selected points, thereby producing irregular convex polygons (Vanderplas and Garvin, 1959). Of the eight figures used, three were four-point shapes (difficulty level 1, on a range of 1 low to 6 high difficulty) and five were six-point shapes (difficulty level 2).

2.2.2. Dual tasks

In the dual task condition, the subject started again by fixating on a cross in the center of the computer screen for 500 ms. Then, a sequence of two dots appeared over eight possible locations, followed immediately by two sequentially presented solid black Vanderplas figures, which appeared in the center of the screen; each stimulus was shown for 250 ms. The subject then fixed the

center cross for 3 s, after which he was given two papers: on one he numbered the eight possible locations according to where the two dots previously appeared, and on the second he numbered the black figures following the order in which they were presented in the center of the screen. For each new trial, the black dots and black figures were alternated for presentation. The sequence started with two dots and two Vanderplas figures, and the test was stopped once the subject failed twice on the same sequence length and for both the spatial and object conditions. Balancing minimized differential effects the order of conditions may have had on performance.

2.3. Statistical analysis

These analyses evaluated working memory in the form of recall for a specific stimulus and its order over increasing sequence lengths. For score calculation, one point was given for every correct response out of a maximum of 12 points.

Statistical analysis included two sets of 2×3 omnibus analysis of variance (ANOVA) with follow-up 2×2 ANOVAs and *t*-tests. Given our hypotheses, we anticipated two possible outcomes. A significant group-by-task interaction, where the schizophrenic group showed an excessively lower performance on the dual task relative to their performance on the single tasks, and relative to the increased difficulty shown by the controls on the dual task, would support the central executive as the unitary structure of working memory. Alternatively, a non-significant group-by-task interaction would support the multiple memory systems model of working memory.

3. Results

3.1. Spatial vs. object vs. dual tasks

3.1.1. Spatial vs. shapes tasks

A $2 \text{ group} \times 3 \text{ task}$ ANOVA (single spatial vs. single shapes vs. dual shapes) yielded significant effects of group ($F(1,24) = 10.692, p = 0.0032$) and task ($F(2,48) = 100.736, p = 0.0001$), but no significant group-by-task interaction ($F(2,48) = 2.211$,

$p=0.1206$) (Fig. 3A). Follow-up analyses indicated that the schizophrenic group had significantly lower scores than the control group on the single spatial measure ($t(24)=2.537$, $p=0.0181$), the single shapes measure ($t(24)=4.144$, $p=0.0004$) and the dual shapes measure ($t(24)=2.133$, $p=0.0433$). Thus, both the schizophrenic and control groups declined on the dual tasks relative to the single tasks, and both groups reached greater sequence lengths on the spatial than object tasks.

The schizophrenic and control groups performed

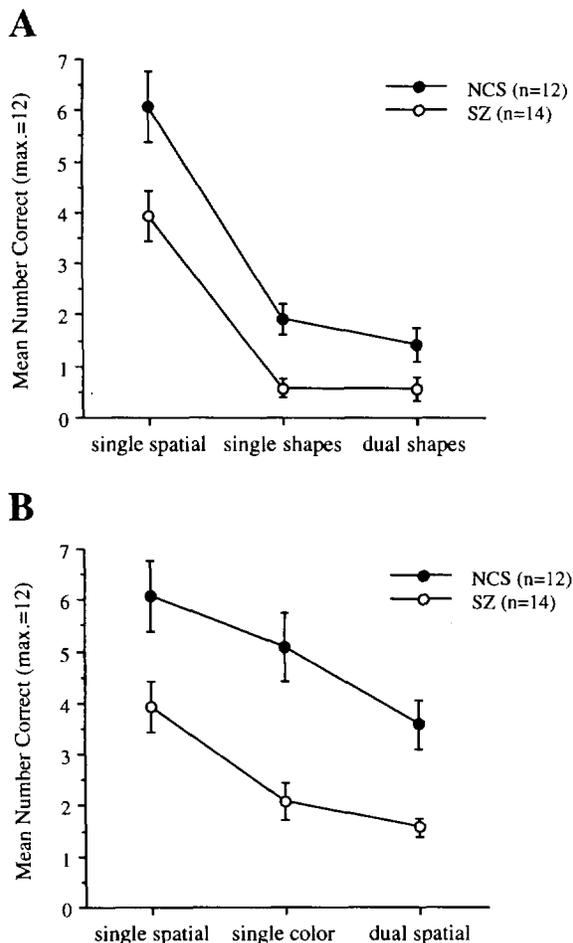


Fig. 3. (A) and (B) Raw scores from the single and dual working memory tasks, as assessed by stimulus and order recall. Each of the two groups showed decreasing recall scores on the object and dual tasks relative to the spatial task. Neither group-by-task interaction was significant.

worse on the single shapes and dual shapes conditions than on the single spatial condition, as indicated by three subsequent 2 group \times 2 task ANOVAs. ANOVA comparing single spatial and single shapes conditions showed both a significant group ($F(1,24)=11.077$, $p=0.0028$) and task ($F(1,24)=102.322$, $p=0.0001$) effect, but no significant group-by-task interaction ($F(1,24)=1.197$, $p=0.2847$); similarly for ANOVA comparing single spatial and dual shapes, group effect ($F(1,24)=7.25$, $p=0.0127$), task effect ($F(1,24)=122.594$, $p=0.0001$) and no significant group-by-task interaction ($F(1,24)=3.329$, $p=0.0805$). ANOVA comparing single shapes and dual shapes indicated only a significant group effect ($F(1,24)=11.928$, $p=0.0021$), but no task effect ($F(1,24)=1.749$, $p=0.1985$) or group-by-task interaction ($F(1,24)=2.04$, $p=0.166$). Mann-Whitney U tests were used to confirm group differences because of the restricted range of scores. Mann-Whitney U tests showed the same group differences as the t -tests for the single shapes ($Z=3.191$, $p=0.0014$), the dual shapes ($Z=1.989$, $p=0.0467$) and the single spatial ($Z=2.324$, $p=0.0201$) conditions.

3.1.2. Spatial vs. color tasks

A second 2 group \times 3 task (single spatial vs. single color vs. dual spatial) ANOVA produced significant effects of group ($F(1,24)=19.699$, $p=0.0002$) and task ($F(2,48)=20.018$, $p=0.0001$), but no significant group-by-task interaction ($F(2,48)=0.978$, $p=0.3836$) (Fig. 3B). Further analyses indicated that the schizophrenics performed significantly worse than the controls on the single spatial measure ($t(24)=2.537$, $p=0.0181$), the single color measure ($t(24)=4.146$, $p=0.0004$) and the dual spatial measure ($t(24)=4.275$, $p=0.0003$). The schizophrenic and control groups scored higher on the color than on the shapes object memory task.

Three follow-up 2 group \times 2 task ANOVAs demonstrate that both groups had significantly lower scores on the single color and dual spatial conditions than on the single spatial condition. ANOVA contrasting single spatial and single color condition yielded both significant group ($F(1,24)=13.814$, $p=0.0011$) and task ($F(1,24)=15.196$, $p=0.0007$) effects, but no significant group-by-task

interaction ($F(1,24)=1.299$, $p=0.2657$). ANOVA comparing single spatial and dual spatial conditions yielded similar results: significant group ($F(1,24)=13.317$, $p=0.0013$) and task ($F(1,24)=40.611$, $p=0.0001$) effects and no group-by-task interaction ($F(1,24)=0.035$, $p=0.853$). Similarly, ANOVA comparing the single color and dual spatial conditions showed significant group ($F(1,24)=29.678$, $p=0.0001$) and task ($F(1,24)=5.741$, $p=0.0247$) effects, but no significant group-by-task interaction ($F(1,24)=1.543$, $p=0.2262$). Mann–Whitney U tests verified the group differences seen with the t -tests for the single color ($Z=3.569$, $p=0.0004$), the dual spatial ($Z=3.451$, $p=0.0006$), and the single spatial ($Z=2.324$, $p=0.0201$) conditions.

3.2. Chance level analysis (Fig. 4A and B)

The expected score, if a subject is performing at chance level, for the single shapes condition is 0.0359, with a variance of 0.0357 and standard deviation (SD) of 0.0505. The mean score for all 14 schizophrenic patients on the single shapes task is 0.571, which is 11 SDs above the expected chance-level score. Thus, we conclude that the schizophrenic patients performed above chance level on the single shapes task, the condition with the lowest scores, and consequently on all other conditions.

3.3. Effect of anticholinergic medication on performance in schizophrenics

To examine the effects of anticholinergic load on test performance, the subgroup of patients with no or low anticholinergic load ($N=6$) was compared with the subgroup of patients with a moderate to high anticholinergic load ($N=8$). No significant subgroup difference was found for any of the five test conditions (p -values range = 0.2004–0.3388). These findings must be interpreted with caution, as a conversion of medication doses to a common standard of chlorpromazine levels would yield stronger results for the effect of anticholinergic load on working memory performance. The small sample size and the poly-pharmacologi-

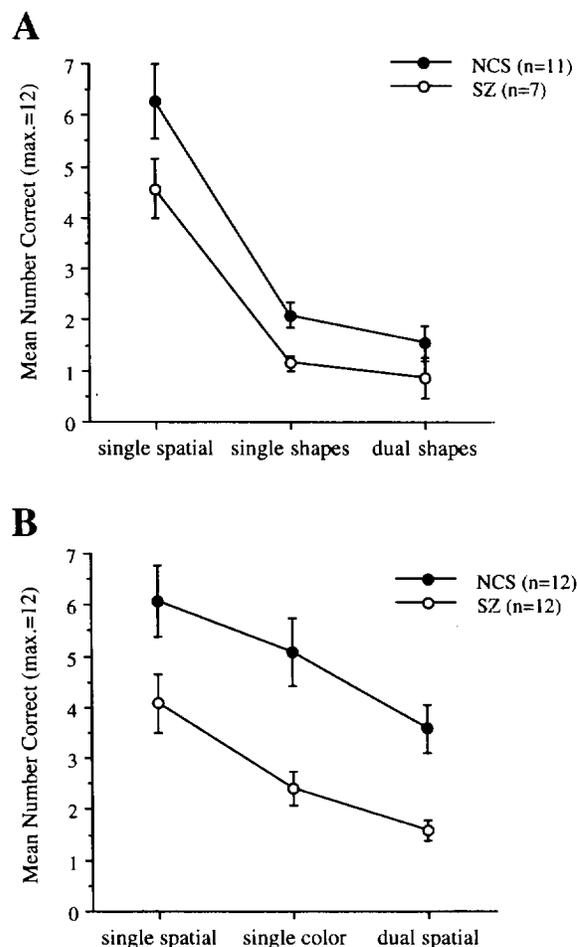


Fig. 4. (A) and (B) The same data were used as for Fig. 3A and B, except that all schizophrenic patients and normal control subjects scoring zero on the single shapes or single color conditions were excluded from the analysis.

cal therapy of most patients in this study do not readily allow for such analysis.

3.4. Effect of history of substance abuse or dependence on performance in schizophrenics

Of the 14 patients, seven had a history of substance abuse or dependence at one time in their life, while the remaining seven had no such history. Significant differences were not detected with t -tests between these two groups for any of the five working memory test conditions (p -values

range=0.0989–0.8558). However, given the small sample size, it is not possible to reliably assess the potential impact of substance abuse on working memory performance in schizophrenic patients.

4. Discussion

The experimental task aimed to elucidate the organization of working memory in patients with schizophrenia, by first examining the spatial and object components separately and then together as a dual task. For spatial and color memory tasks, both the schizophrenic and the control groups scored higher on the single component task than on the dual task. Also, both groups performed better on the spatial task than on the object tasks and on the dual spatial task than on the dual shapes task. Within the object tasks, both the schizophrenic and the control groups achieved lower scores on the shapes condition than on the color condition. Importantly, neither the single spatial vs. single shapes vs. dual shapes condition nor the single spatial vs. single color vs. dual spatial condition yielded a significant group-by-task interaction. These results indicate that the schizophrenic patients are not performing significantly worse on the dual task than on the single tasks relative to the controls. Therefore, the lack of group-by-task interaction provides no support for a dysfunction of the central executive in schizophrenic patients; rather, working memory seems to comprise multiple, relatively independent systems.

Both spatial and object working memory were significantly impaired, suggesting that the two memory systems are affected in schizophrenia. However, both the schizophrenic and the control groups had lower scores on tests of object than of spatial memory. Given the difference in performance in the control group, it appears that the object memory tasks were more difficult than the spatial memory tasks. The lack of group-by-task interaction, however, indicates that the schizophrenic group was not disproportionately affected by this difference in difficulty level in object memory relative to the controls.

The schizophrenic group performed significantly worse than the control group on all tasks, whether based in memory for spatial locations or objects. These observations are consistent with other studies, which report a variety of working memory deficits, observed in oculomotor and haptic delayed-response tasks (Park and Holzman, 1992), object alternation and delayed alternation tasks (Seidman et al., 1995), word recall following short distractor-filled retention intervals (Fleming et al., 1995), and listening and computation spans (Stone et al., in press). Two of these studies also showed that even when schizophrenic patients demonstrated deficits in immediate memory, as assessed by digit span, this impairment did not account for the concomitant deficits in working memory (Gold et al., 1997; Stone et al., in press). Thus, the working memory impairment may not be simply the result of generalized cognitive compromise, but rather may be independent of other processing deficiencies (e.g., attention) in schizophrenia.

From primate studies, Wilson et al. (1993) proposed associations of the posterior parietal cortex with spatial conceptualization and of the inferior temporal cortex with object discrimination; both regions are hypothesized to share ties with the dorsolateral prefrontal cortex. Our study revealed significant spatial and object working memory deficits for schizophrenic patients, possibly resulting from cortical volume deficits of the prefrontal cortex observed in schizophrenia (Selemon et al., 1995; Sullivan et al., in press; Schlaepfer et al., 1994). However, the lack of group-by-task interaction indicates that schizophrenic patients are no worse while performing a dual task than single tasks, engaging spatial and object memory pathways. This result reflects a parallel observation in Parkinson's patients, which, like schizophrenia, affects striatofrontal pathways (Alexander et al., 1986). Fournet et al. (1996) assessed working memory in Parkinson's patients using a 'dual task paradigm combining verbal, visual, or spatial span with two conditions of articulatory suppression', similar in part to the dual task used in this study. These authors concluded that the central executive was not impaired in patients with Parkinson's disease. Similarly, we speculate that our findings do not support dysfunction of the central executive

in schizophrenia, but rather disruption of multiple systems of working memory.

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