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A study of visual and auditory verbal working memory in schizophrenic patients compared to healthy subjects

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Abstract Impaired working memory (WM) performance is considered as a central feature of schizophrenia. Divided into two components, verbal and spatial, WM has been shown to involve frontal and parietal regions. Verbal WM can be tested either visually or aurally. The present study aimed to test schizophrenic patients in both visual and auditory verbal WM in order to assess a possible distinct pattern of alteration of these two modalities. Twenty-four schizophrenic patients and 24 healthy controls were compared with 2-back continuous visual and auditory verbal WM testing. Both groups were also tested on a neuropsychological battery including Wisconsin Card Sorting Test (WCST). Schizophrenic patients were less efficient in both verbal WM tests. When taking age and educational level as covariates and both WM modalities as dependent variables, there was no differential effect of modalities across groups. In further exploratory analyses, partial correlations brought association between verbal WM and psychosocial adaptation, WCST and length of illness. These results suggest a similar pattern of alteration of both modalities of verbal WM in schizophrenic patients. The implications of this finding are discussed.

Key words Schizophrenia · Working Memory · Wisconsin Card Sorting Test

Introduction

Clinical and experimental evidence support the presence of neurocognitive alterations in schizophrenia. Since the clinical description of schizophrenia by Kraepelin (1919), cognitive abnormalities have been considered as a central feature of this disorder. Schizophrenic patients exhibit neuropsychological impairment in various functions (for review, see Goldberg and Gold 1995). Abnormalities are particularly obvious in attention (Mirsky 1988), memory (Saykin et al. 1991) and executive functions (Braff et al. 1991). Overall, neuropsychological impairment and its evolution with age, in schizophrenia, are consistent with the concept of a "static encephalopathy". They are in agreement with the idea of a non-progressive neurodevelopmental lesion, as described by Weinberger (1987). Clinical and outcome features are different across gender for schizophrenic patients, with females being known to have generally a better prognosis, in various cultural and ethnic backgrounds (Huguelet et al. 1994). Studies comparing neuropsychological results between males and females have reported inconsistent results (Goldberg and Gold 1995). However, a recent study (Goldstein et al. 1998) demonstrated that schizophrenic women are less impaired than men, compared to gender-matched normal subjects.

Association between neuropsychological deficits and specific morphological and functional alterations support the involvement of a frontal-temporal dysfunction in schizophrenic patients (Weinberger et al. 1992). The Wisconsin Card Sorting Test (WCST), which is considered to reflect frontal integrity (Park and Holzman 1992), has been largely used to study the cognitive impairment of schizophrenic patients and the brain regions correlated with their performances. Prefrontal cerebral blood flow and metabolism have been shown to be altered in schizophrenic patients, particularly when performing cognitive tasks like WCST (Weinberger et al. 1986, Berman et al. 1992). The WCST implies several successive cognitive operations (concept formation, hypothesis testing, set shifting). This makes WCST correspond to several cognitive processes, probably mediated by distinct anatomic systems (Gold et al. 1997). The interpretation of the results of this test may therefore be hazardous. Thus, more specific and simple cognitive tests are needed. Tests implicating working memory (WM) may play this role, as WCST requires the use of WM, in addition to other operations. WM, defined by Baddeley (1992) as a "...system that is necessary for the concurrent storage and manipula-

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tion of information...", is considered as a tripartite system. A central executive, assumed to be an attentional-controlling system, is supplemented by two "slave systems". One of them is called articulary or phonological loop and is supposed to deal with the maintenance of speech-based information. The other is the visuospatial sketch pad which performs the setting and the manipulation of visuospatial imagery. Thus, WM combines attention, memory, conceptualizing and planning. WM can be evaluated through its two components, verbal and spatial WM. Positron emission tomography (PET) and functional Magnetic Resonance Imaging (fMRI) studies have been helping to localize brain regions involved in WM. Paulesu et al. (1993), with [^{15}O] PET, associated the phonological processing of a verbal memory task with activation of bilateral (although left > right) Brodmann's areas (BA) 44, 40, 22/42. Broca's area (which is located at BA 44) was considered by the authors as the subvocal rehearsal system, and BA 40 (a part of the inferior parietal lobule) as the phonological store. Jonides et al.(1993) studied with the same PET technique the activation induced by a spatial WM task. Regional cerebral blood flow was increased in the right hemisphere, in prefrontal (BA 47), occipital (BA 19), parietal (BA 40) and premotor (BA 6) cortices. These results were consistent with Baddeley's conceptualization of WM. Cohen et al. (1997), using fMRI, studied the activation induced by verbal continuous WM tasks. The temporal resolution of fMRI allowed the examination of the dynamics of regional activation. The pattern of activation showed the association of dorsolateral prefrontal cortex (BA 46/9), other frontal regions (BA 8, 44), and parietal regions (BA 7, 40) with memory load. All in all, the precise regions involved may vary, depending on the nature of the WM task (verbal vs. visual). BA 44 may represent the central executive of the frontal lobe. More posterior regions, also specific to the kind of WM involved, may be principally used in sensory and perceptual processes, as well as in partial memory functions.

Some neuroreceptors are likely to be involved in working memory. D1 receptors may play an important role in these functions, with a biphasic effect for the D1-antagonists and a triphasic effect for the D1-agonists (Arnsten 1997). In the study of Sawaguchi and Goldman-Rakic (1991), the blockade of rhesus prefrontal D1 receptors was associated with an alteration of working memory. The deficit was dose-dependent. The authors came to the conclusion that prefrontal D1 receptors may be involved in memory processes, probably through projections to the thalamus, caudate nucleus and superior colliculus. 5HT2a receptors may also be implicated, according to the results of the Green et al. (1997) study on the effect of risperidone, a 5HT2a antagonist, on verbal WM in schizophrenic patients. The study of Gallhofer et al. (1996), showing an improvement on the maze test in schizophrenic patients treated with atypical antipsychotic agents compared with conventional neuroleptics also suggests an implication of the blockade of 5HT2a. The influence of 5HT2a blockade on working memory may be the consequence of the interaction of 5HT2a and dopamine. Indeed, as discussed by Kapur and Remington (1996), 5HT blockade disinhibits dopamine activity, not only in the striatum but also in the prefrontal cortex. Golman-Rakic and Selemon (1997), in an integrative view, suggest an involvement of glutamate, GABA, serotonin, and dopamine in the WM alterations encountered in schizophrenic patients.

Verbal WM has been found altered in schizophrenic patients by Gold et al. (1997). They developed an auditory WM task, the letter-number (LN) span. Compared to control subjects, the performance of schizophrenic patients was inferior to that of controls in LN span. The results of this test were correlated to WCST performances. Moreover, covariance analysis with LN span eliminated the WCST differences between the two groups. The authors concluded that impairment of WM may be involved in many of the cognitive deficits linked to schizophrenia. Thus, WM, at least in its verbal component, represents a relatively "pure" process which is relevant to the study of schizophrenia. Verbal WM alterations may be specific to schizophrenic patients compared to alcoholic patients (Sullivan et al. 1997) or to patients with obsessive-compulsive disorder whose results on WM tasks were not altered (Martin et al. 1995). Park and Holzman (1992) demonstrated a deficit in spatial WM in medicated schizophrenic patients. Their deficit, relative to control subjects and patients with bipolar disorder, were present both in an oculomotor and a haptic version of the task used. O'Donnell et al. (1996) found that schizophrenic patients were less accurate than control subjects on trajectory tasks (which imply visuospatial WM). Other authors have underlined impairment in visuospatial WM among schizophrenic patients (Keefe et al. 1995). Carter et al. (1996) found unmedicated schizophrenic patients impaired in a spatial WM task. This alteration was correlated with negative symptoms. Fleming et al. (1997) used three spatial tasks to study 32 schizophrenic patients compared to 27 controls. Basic spatial analytic abilities of the patients appeared intact, but tasks involving memory were markedly insufficient. The authors conclude that the passive visual store and the active spatial rehearsal may be disrupted in schizophrenic patients. Park et al. (1995) demonstrated alteration in spatial WM performances in schizophrenic patients, as well as in first-degree relatives of schizophrenic patients. This latter group performed worse than control subjects but was better than the patients' group.

There may be a verbal WM system specific to auditory material, i.e. distinct from the verbal WM system involved when information is presented visually. Schumacher et al. (1996) failed to show with [^{15}O] PET that verbal WM is modality dependent as activation by visual or auditory tasks revealed a complete overlap between the modalities. Nevertheless, as some case reports of brain-damaged patients have shown a differential impairment of verbal WM according to modality, there is need to address whether schizophrenic patients show a different pattern of alteration for the two modalities. This aspect led us to assess the two modalities of verbal WM performances in this diagnostic group compared to healthy subjects. These data allowed us to test whether alteration encountered was different for aurally or visually verbal WM testing. Furthermore, WM performances in patients were correlated with other measures like WCST, psychosocial adaptation, negative symptoms, and other clinical and sociodemographic features.

Materials and methods

Twenty-seven outpatients, 18–50 years old with a diagnosis of chronic psychotic disorder underwent testing as part of their clinical evaluation. These patients were drawn from an outpatient clinic and were clinically stable when tested. For the purpose of this study, patients were eligible if they met the following criteria: a) a diagnosis of schizophrenia or schizoaffective disorder as defined by DSM-IV (American Psychiatric Association 1994). Diagnosis was made by at least two clinicians, i.e. a ward psychiatrist and a senior psychiatrist, following review of medical records, interview with the patient and an extended period of clinical observation, b) no formally diagnosed psychiatric disorder other than a current chronic schizophrenia or schizoaffective disorder, c) no current or past history of neurological illness and d) no acute medical illness. As three patients did not fulfil these criteria, our group was constituted of 24 patients. Twenty-one were right-handed. Twenty-four healthy 18–50 year old subjects were recruited for comparison. All subjects denied any history of neurological or psychiatric illness on interview. None of them had a first-degree relative with schizophrenia. Twenty-one were right-handed. Characteristics of the sample are reported in Table 1. All subjects gave their informed consent prior to their inclusion in the study.

All subjects received a neuropsychological evaluation including a computerized version of WCST (subtest of Coglab, Spaulding et al. 1989, Spaulding et al. 1994). This test brings three results: number of trials to complete five series, perseverative answers and random answers. The Standard Progressive Matrix (SPM 38) (Raven 1938), in its short version (Thuillard and Assal 1991), was also administered. The patients' group underwent a clinical evaluation with the PANSS (Positive and Negative Syndrome Scale, Kay et al. 1987), and social evaluation with the GAS (Global Assessment Scale, Endicott et al. 1976) and the MRSS (Morningside Rehabilitation Status Scale, Affleck and McGuire 1984). The MRSS includes four subscales: 1) Dependency; 2) inactivity in occupation and leisure; 3) social integration/isolation, and 4) current symptoms and deviant behaviour. All but two patients were treated with neuroleptics. The doses of neuroleptics were converted into equivalent doses of chlorpromazine, as described by Calanca et al. (1997).

Both groups received two continuous verbal WM testings. The visual verbal WM testing involves continuous presentation of a hundred digits on a computer screen (Zimmerman et al. 1994). The subject's task is to indicate with a key press if each digit presented is identical to the one presented two digits previously in the sequence. We developed an auditory version of this task which involves the auditory presentation by an examiner of a series of a hundred digits. The subject is asked to respond if each digit read is identical to the one read two digits previously in the sequence. Both tests give two results: the number of correct answers (number of digits correctly identified as the same as the one presented two digits previously in the sequence; maximum score is 15), and the number of errors (number of digits falsely identified as the same as the one presented two digits previously in the sequence). The order of presentation of both WM tests was counterbalanced across subjects.

The statistical analyses addressed the comparison of WM performances between groups and the possibility of a differential impairment of auditory and visual verbal WM. As groups appeared to be different in age and education level, we performed an overall ANCOVA, using groups (i.e. schizophrenia vs. healthy subjects) as between subjects factor, age and educational level as covariates, and both modalities of verbal WM correct answer scores as dependent variables. For the schizophrenic patients, correlation between WM performances and the other variables were performed using partial correlations after correction for age and education. All statistical analyses were carried out using Systat version 5.0 (Systat Inc. Evanston, Illinois 1992).

Table 1 Sociodemographic, clinical and neurocognitive characteristics of the sample

Characteristics	Schizophrenic patients (*n* = 24)	Controls (*n* = 24)
Age*	33.1 (9.3)	28.0 (7.1)
Gender (M/F)***	19/5	11/13
Education (years)**	10.8 (3.2)	16.0 (2.8)
Length of illness (months)	128 (116)	...
Number of hospitalizations	4.2 (4.1)	...
PANSS		
Total	61.2 (11.4)	...
Positive symptoms	12.6 (4.4)	...
Negative symptoms	19.1 (6.2)	...
General psychopathology	29.6 (7.1)	...
GAS (past year)	51.3 (8.2)	...
MRSS (total)	15.4 (3.5)	...
Dependency	3.3 (1.6)	...
Inactivity	4.6 (1.5)	...
Isolation	3.8 (1.2)	...
Current symptoms	3.7 (0.9)	...
Schizophrenic disorder subtype		
Disorganized (295.1)	5	...
Paranoid (295.3)	8	...
Undifferentiated (295.9)	4	...
Residual (295.6)	3	...
Schizoaffective (295.7)	4	...
Chlorpromazine equivalent (mg)	210 (366)	...
SPM38**	19.1 (5.1)	25.0 (1.9)
WCST		
Number of trials**	62.4 (20.9)	36.6 (5.9)
Perseverations (%)**	28.6 (8.0)	18.0 (6.1)
Random (%)**	27.4 (11.3)	12.5 (4.7)

PANSS: Positive and Negative Syndrome Scale; GAS: Global Assessment Scale, MRSS: Morningside Rehabilitation Status Scale; SPM38: Standard Progressive Matrix, 1938; WCST: Wisconsin Card Sorting Test
Student t-test, *$p \leq 0.05$, **$p \leq 0.001$, ***Fisher exact test, $p \leq 0.05$

Results

Normal subjects were significantly younger and better educated than the patient group (Table 1). Gender was not equally distributed across groups (Fisher exact test p: 0.04). This led us to assess gender differences in both groups for all variables. Using non-parametric tests (i.e. Mann-Whitney test), we did not find any significant difference. Accordingly, only age and educational level were included in our overall ANCOVA. The schizophrenic and control groups differed significantly on SPM38 and WCST measures.

Table 2 Working memory scores

	Schizophrenic patients	Controls
Visual verbal working memory		
Correct answers	11.0 (2.5)	12.8 (2.2)
Errors	8.5 (12.6)	1.6 (1.7)
Auditory verbal working memory		
Correct answers	9.9 (3.4)	13.8 (1.5)
Errors	8.2 (13.9)	2.5 (2.1)

Table 3 ANCOVA for visual and auditory working memory

	df	F	p
Between subjects			
Group	1,44	7.2	0.01
Age	1,44	7.8	0.008
Educational level	1,44	2.1	0.15
Within subjects			
Modality	1,44	3.1	0.08
Modality x group	1,44	0.003	0.96
Modality x age	1,44	0.07	0.79
Modality x educational level	1,44	5.6	0.02

Table 2 shows visual and auditory verbal WM correct answers and errors score. Schizophrenic patients performed worse than controls for all measures. As both groups differed in educational level and age, we performed an ANCOVA including these variables as covariates, with both modalities (i.e. visual and auditory correct answers) as dependent variables, and diagnosis (patients vs. healthy subjects) as grouping factor. This computation was made for correct answers only as they had similar variance across groups and modalities. As seen in Table 3, ANCOVA revealed a group effect for verbal WM performances (F: 7.2, p: 0.01). Age effect was also significant (F: 7.8, p: 0.008). There was no significant interaction between modality (visual vs. auditory) and group. The only significant interaction was between modality and educational level (F: 5.6, p: 0.02). This result reflects the existence of a positive correlation between educational level and auditory verbal WM, but not with visual verbal WM, i.e. better education brought better results only on the task presented aurally by an examiner.

To clarify the relationship between WM scores and neuropsychological and clinical variables, partial correlations were performed in schizophrenic patients, with age and education as covariates (Table 4). Visual verbal WM errors were correlated with WCST number of trials and length of illness. Auditory verbal WM correct answers were positively correlated with GAS, i.e. good performances were associated with better psychosocial adaptation. However, because of the high number of correlations, results did not reach significance after correction for multiple testing.

Discussion

In this study, both visual and auditory verbal WM were altered in schizophrenic patients when compared to healthy subjects. This impairment did not appear to be modality-dependent. The WM deficits encountered here are in accordance with the results of Gold et al. (1997) who found

Table 4 Partial correlations for working memory in the schizophrenic patients, after correction for age and education

	Visual verbal working memory		Auditory verbal working memory	
	Correct answers	Errors	Correct answers	Errors
PANSS				
Total	–0.37	–0.25	0.36	0.01
Pos. symptoms	–0.07	–0.14	0.06	0.16
Neg. symptoms	–0.45	0.03	0.33	–0.27
Gen. psychopath.	–0.25	–0.31	0.31	0.05
MRSS				
Total	–0.25	–0.02	0.06	0.32
Dependency	–0.14	0.00	0.24	0.26
Inactivity	–0.22	0.02	0.00	0.31
Isolation	–0.29	–0.11	0.11	0.05
Current symptoms	0.02	0.02	–0.40	0.19
GAS	0.04	–0.33	0.61**	–0.30
Medication	–0.06	–0.22	0.28	–0.09
SPM38	0.17	–0.41	–0.19	0.04
WCST				
Number of trails	–0.18	0.69*	0.10	0.08
Perseverations (%)	–0.04	0.41	0.03	–0.01
Random (%)	–0.17	0.41	0.01	0.06
Length of illness	0.18	0.61**	–0.24	0.24
Number of hosp.	–0.19	0.19	–0.22	–0.21

PANSS: Positive and Negative Syndrome Scale; GAS: Global Assessment Scale; MRSS: Morningside Rehabilitation Status Scale; SPM38: Standard Progressive Matrix, 1938; WCST: Wisconsin Card Sorting Test
*p: 0.003, **p: 0.012 (p values, without correction for multiple comparison)

auditory verbal WM to be altered in schizophrenic patients. Park and Holzman (1992) in their study on spatial WM also administered a verbal WM task (digit span test) and did not find any impairment. However, this task did not involve the manipulation of the information stored, contrary to the task used by Gold et al. (1997) and the one used in our study. Wexler et al. (1998) reported that auditory verbal WM was severely impaired in schizophrenic patients, while auditory nonverbal WM (i.e. a tone delayed discrimination task) remained intact. Karatekin and Asarnow (1998) studied young patients with childhood-onset schizophrenia. They showed that their performances were altered on the Digit Span of the Wechsler Intelligence Scale (which is administered aurally) compared to normal children. This result, in contradiction with the Park and Holzman study (1992) mentioned above, may be explained by the fact that childhood-onset schizophrenia represents a severe form of schizophrenia. Thus, these patients may feature alterations even in a task involving no manipulation of information.

The interpretation of the fact that WM deficit does not appear to be modality-specific remains difficult. These results are in agreement with data on brain imaging reported above (Schumacher et al. 1996) showing no modality-specific verbal WM systems. However, studies of brain-damaged patients brought evidence for modality-specific systems (McCarthy and Warrington 1990). Structural imaging studies (e.g. Cannon et al. 1998) show alterations in temporal structures in schizophrenic patients. In addition to prefrontal dysfunction, they feature alteration of the auditory verbal circuits which are located in superior temporal and inferior parietal cortex (Schumacher et al. 1996). An auditory WM deficit may be caused by a perceptual or encoding dysfunction in the information processing sequence as demonstrated by Javitt et al. (1997) in their study on auditory sensory memory information in schizophrenia. In their study, Wexler et al. (1998) concluded that schizophrenic patients display deficits in auditory verbal memory. Furthermore, for some patients, deficits were attributed to perceptual and encoding dysfunction in addition to verbal WM deficits. Thus, these data are not confirmed by our results. This could be accounted for by the relatively large WM deficit encountered herein, in the presence of slighter temporal abnormalities. Accordingly, in addition to our relatively small sample size, a potential differential impairment may have been masked. Finally, we cannot exclude that the lack of modality effect may be due to the fact that one WM testing was administered by computer whereas the other was aurally administered by one of the authors.

As mentioned before, analysis of correlation needs to be considered with caution due to the exploratory nature of such data. We found a correlation between auditory verbal WM and psychosocial adaptation (i.e. GAS) as reported by Green et al. (1996). The correlation between visual verbal WM error score and WCST can be compared with the results of Gold et al. (1997) who found a strong correlation between an auditory WM task and WCST performances. We can interpret our data as the confirmation that the WM process, as part of the WCST cognitive operations, is altered in schizophrenic patients. Correlation of visual verbal WM with length of illness is difficult to interpret as it contradicts data showing no evolution of neurocognitive deficit in schizophrenia.

The present study has some limitations. A confounding effect of medication may entail the verbal WM alteration encountered in schizophrenic patients. However, our data do not show any significant correlation between WM scores and doses of medication. Carter et al. (1996) found alterations in schizophrenic patients who had not been treated for at least ten days. Thus, it is likely that WM deficit reflects mostly the pathology associated with schizophrenia itself. Nevertheless, medication may influence cognitive performance, either in worsening it or in the sense of improvement. In the particular case of WM, classical neuroleptics and clozapine do not seem to have a great influence (Goldberg and Weinberger 1995, Murphy et al. 1997) whereas risperidone has brought some encouraging preliminary results (Green et al. 1997). In our study, the lack of prospective design makes it impossible to address this topic. Indeed, the patients treated with risperidone may have received it on account of distinct characteristics which may be altered by the treatment itself and impossible to assess in our protocol. The WM alterations encountered here could come from other biases. Schizophrenic patients and healthy subjects differed in their age and educational level. This led us to perform an overall ANCOVA taking educational level and age as covariates in order to address this bias. The relationship between WM scores and educational capacities is complex. Lack of education could have slightly lowered the WM capacities of schizophrenic patients but it is likely that WM deficit may be in itself partly responsible for educational difficulties. Thus, matching the sample for educational level would have selected either a “supernormal” population of schizophrenic patients, or a “subnormal” population of healthy subjects.

This study indicates that schizophrenic patients are less efficient in both visual and auditory verbal WM tests. In addition, these results do not suggest a modality-specific pattern of impairment in these patients. As these data were drawn out of a relatively small sample, more research is needed in order to address this topic in a more comprehensive way.

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