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Remitted schizophrenia-spectrum patients with spared working memory show information processing abnormalities

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Abstract Working memory and information processing abnormalities are often reported in schizophrenia. The aim of this study was to examine visual backward masking (BM) functions in remitted schizophrenia-spectrum patients with spared working memory functions. Seventy-two patients with DSM-IV schizophrenia-spectrum disorders were screened using the Wisconsin Card Sorting Test (WCST) and the digit span forward/backward tasks. Patients with spared WCST and digit span performances were selected and administered a spatial working memory test and two BM procedures (target identification and location). The schizophrenia-spectrum group with spared WCST and digit span performances included individuals with schizophreniform disorder (N=11), schizophrenia (N=2), and schizoaffective disorder (N=2). These patients were clinically remitted and demonstrated spared IQ, normal spatial working memory, and relatively high psychosocial functioning. However, there was a significant impairment in the BM procedure, most prominently in the target location task and at short interstimulus intervals. These results suggest that the BM dysfunction is a trait marker of schizophrenia-spectrum disorders and may be present in the absence of working memory abnormalities.

Key words Schizophrenia · Schizophreniform disorder · Information processing · Backward masking · Working memory · Trait marker

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Introduction

Neurocognitive approaches to schizophrenia provided two leading hypotheses. The first hypothesis emphasizes the dysfunction of voluntary and controlled mental activities. A frequently cited theoretical framework integrating these higher-level deficits focuses on the anomalies of working memory. According to Baddeley (1992), working memory can be decomposed to two slave systems and the central executive. The two slave systems are responsible for the active maintenance of information about objects and their location (visuo-spatial sketchpad) and for the on-line representation of verbal materials (phonological loop). The central executive is devoted to the manipulation and reorganization of maintained information in order to accomplish goal-directed planning and problem solving. Several studies have provided compelling evidence that virtually all aspects of working memory are impaired in schizophrenia, depending on the task used and the clinical characteristics of patients included (Goldberg et al. 1987; Park and Holzman 1992; Fleming et al. 1995, 1997; Morice and Delahunty 1996; Gold et al. 1997; Spindler et al. 1997; Wexler et al. 1998; Salamé et al. 1998; Kéri et al. 1999; Glahn et al. 2000). The biological substrate of working memory includes a large-scale neuronal network in which the prefrontal cortex plays a central role (Smith and Jonides 1999). Indeed, patients with schizophrenia usually show abnormal prefrontal activities during various working memory tasks in accordance with macrostructural and neuropathological alterations (Goldman-Rakic and Selemon 1997; Harrison 1999; Berman and Weinberger 1999).

The second hypothesis is concerned with early perceptual and attentional dysfunctions in schizophrenia (Nuechterlein and Dawson 1984; Braff 1993). For example, in the visual backward masking (BM) paradigm a briefly presented target is immediately followed by a second, irrelevant stimulus (the mask), which inhibits the detection of the target. Patients with schizophrenia often show lower performances in the BM paradigm compared with normal controls, which is interpreted as a sign of impaired visual information processing (Saccuzzo and Braff 1981; Green et al. 1994 a, 1994 b; Cadenhead et al. 1998). However, the relationship between working memory and information processing hypotheses is less clearly understood. According to Braff (1993), attention and information processing anomalies are fundamental trait markers of schizophrenia, and disturbances in cognition and neuropsychological functions are secondary consequences of these basic impairments. It has been shown that remitted patients with schizophrenia exhibit BM dysfunctions (Miller et al. 1979; Green et al. 1999; Kéri et al. 2000), which indicates its potential independence from clinical symptoms and supports the view that the BM deficit is a trait marker of schizophrenia.

The few studies investigating BM performance and higher-level cognitive disturbances revealed a relationship among negative symptoms, executive dysfunctions, and BM impairments (Butler et al. 1996; Voruganti et al. 1997; Wong et al. 1997). It is essential to take into consideration, however, that correlation data do not necessarily mean that working memory and information processing anomalies always appear together in a parallel fashion. Instead of a pure correlation approach, which is susceptible for statistical confounding factors, we selected patients with schizophrenia-spectrum disorders who exhibited normal performances in the digit span forward/backward tasks and the Wisconsin Card Sorting Test (WCST), each designed to investigate different aspects of working memory (Heaton et al. 1993; Wildgruber et al. 1999; Conklin et al. 2000). The patients who passed this selection phase were administered an additional spatial working memory test and two BM procedures, a target identification and a target location task. We had two initial hypotheses. First, patients with intact working memory are characterized by less severe clinical symptoms and higher levels of intellectual and psychosocial functioning. Second, if the BM dysfunction is a trait marker of schizophrenia-spectrum disorders – independent of clinical symptoms and higher-level cognitive impairments – the patients will show lower performances in these tests in comparison with the healthy control subjects.

Methods

Subjects

From 72 patients with DSM-IV schizophrenia-spectrum disorders (American Psychiatric Association 1994), we selected the subjects with spared working memory, as indexed by the WCST and digit span measures. The inclusion criteria were test performances better than 1.5 SD below the control mean and the lack of medical conditions that could impair brain function (neurological disorders, head injury, diabetes mellitus and other endocrine disturbances, severe renal, cardiac and pulmonary diseases, history of electroconvulsive therapy and substance abuse). Fifteen patients met the criteria (schizophreniform disorder (N=11), schizophrenia (N=2, duration of illness: 2 and 7 years), and schizoaffective disorder (N=2, duration of illness: 5 and 8 years). All patients were in psychotic remission (no score on hallucinations, unusual thought content, and conceptual disorganization according to the extended BPRS). Twelve patients (the 11 individuals with schizophreniform disorder and 1 patient with schizoaffective disorder) had no score above 3 on the negative symptom items (blunted affect, motor retardation, emotional withdrawal) (Green et al. 1999). The 2 patients with schizophrenia and the 1 patient with schizophreniform disorder were receiving antipsychotic medication at the time of testing (olanzapine 10 and 20 mg/day for the schizophrenia patients and thioridazine 25 mg/day for the schizophreniform patient). One patient with schizoaffective disorder was receiving lithium (1000 mg/day). Ten patients were non-medicated for more than 6 months. The control group consisted of 34 healthy volunteers without any history of psychiatric or neurological disorders. All participants were explored by expert clinicians and received the Present State Examination (Wing et al. 1974). All participants had normal or corrected-to-normal visual acuity. Student's t-test indicated no significant differences between the patients and controls regarding age, education, and IQ ($p > 0.1$) (Wechsler 1981). For the GAF scores, there was a marginally significant difference ($t(47)=1.98$, $p=0.054$) (Table 1).

Procedure

Wisconsin Card Sorting Test (WCST)

In the WCST, subjects are requested to sort test cards to one of four key cards. The geometric forms on the cards have different shape, color, and number. From these features, only one can be used for sorting (e. g. test cards should be matched to the key card with the same color). Subjects receive feedback to ascertain the categorization rule, which shifts after a number of successful decisions (e. g. from color to shape). The number of categories completed and the number of perseverative errors were the dependent measures (for details, see Heaton et al. 1993).

Digit span forward and backward

In the digit span forward test of the WAIS-R, increasingly longer strings of numbers are recalled (1–9 digits) (Wechsler 1981). In the backward version, subjects repeat the numbers in reverse order. Span length is defined as the number of digits recalled correctly before two strings of the same length were failed.

Tab. 1 Clinical, demographic, and neuropsychological characteristics of the participants

	Schizophrenia-spectrum patients (N=15)	Control subjects (N=34)
Male/female	6/9	15/19
Age (years)	34.3 (5.9)	33.6 (5.0)
Education (years)	11.3 (2.6)	12.8 (3.5)
GAF	74.5 (10.9)	81.5 (11.6)
IQ	106.8 (5.9)	110.1 (7.9)
WCST-CAT	4.8 (0.7)	5.1 (0.9)
DIG-FORW	7.1 (1.0)	7.4 (1.0)
DIG-BACK	6.0 (1.5)	6.4 (1.1)
SWM	6.0 (1.7)	6.7 (1.4)

Data are mean (standard deviation) with the exception of male/female ratio. *GAF* Global Assessment of Functioning; *WCST-CAT* Wisconsin Card Sorting Tests, categories completed; *DIG-FORW* digit span forward; *DIG-BACK* digit span backward; *SWM* spatial working memory (max=12)

Spatial working memory

A trial began with the presentation of a fixation point for 500 ms, which was followed by a sequence of dots, each exposed for 250 ms. The dots appeared in one of the eight locations around an oval shape. After the presentation of dots, the fixation point returned for 3 s. Then, the participant was given a sheet of paper and was asked to number the location of dots according to their sequential appearance. The sequence length increased from 2 to 7 dots and two trials were presented for each sequence length. The test was stopped when the subject was unable to complete both trials at a given length. The maximum score was 12 (Spindler et al. 1997).

Visual backward masking

In the target identification test, the subject's task was to recognize a letter, while in the target location task the spatial position of a letter must have been reported. Stimuli were presented on a monitor controlled by an IBM compatible PC. A small fixation point was present in the middle of the screen throughout the whole experiment. Participants were exposed to 1 of 4 letters (C, O, Q, S) (size: 0.5°of visual angle), which appeared at 1 of 4 locations set at 2.5°of visual angle from the central fixation point (top, bottom, left, right). The task was to press the appropriate keys. The presentation of letters and their locations were randomized. The mask consisted of overlapping X letters, covering all possible target locations. The background luminance was 100 cd/m^2, the luminance of the stimulus area (both target and mask stimuli) was 75 cd/m^2. The luminance of the target and mask was approximately 10 cd/m^2.

In the target identification test, the exposure time of the target was 14 ms, while that of the mask was 28 ms (high energy masking condition where the energy of the mask is defined as the light intensity x duration). In the target location test, the duration of the mask was identical to that of the target (14 ms). The interval between target offset and mask onset (interstimulus interval, ISI) was set at 5 levels: 14, 28, 42, 70, and 98 ms. Twelve targets were presented at each ISI in a pseudo-randomized fashion, that is, the same ISI was never presented twice in succession. Before the test, each participant was provided enough time to become familiar with the experimental setup. In a practice trial, subjects identified 20 target letters without a mask to ensure that they understood the task (for methodological details, see Green et al. 1994 a, 1994 b, 1997).

Results

Working memory

As expected on the basis of our selection process, t-tests indicated no significant between-group differences in the WCST and digit span tasks. In addition, the patients also showed relatively intact spatial working memory functions ($p > 0.1$) (Table 1). Results were similar when the medicated patients were excluded or when only the individuals with schizophreniform disorder were included.

Visual backward masking (BM)

All participant were able to identify more than 17 targets in the no-mask condition. The results of a 2 (group) by 2 (type of task) by 5 (ISI) analysis of variance (ANOVA) are shown in Table 2. Scheffé's tests conducted on the group by task type interaction indicated that the patients with schizophrenia-spectrum disorders were impaired in both the target identification and target location conditions ($p < 0.01$ and $p < 0.0001$, respectively). However, the deficit was more severe in the target location task despite the fact that the two conditions did not differ in difficulty (there was no main effect of task) (Fig. 1, Table 2).

To further explore the group by ISI interaction, a contrast was calculated between short ISIs (14, 28, and 42 ms) vs. long ISIs (70 and 98 ms). The reason for this comparison was that short ISIs (< 60 ms) are thought to reflect early sensory-perceptual processes, while long ISIs are more related to attentional functions (Green et al.

Tab. 2 Results of the analysis of variance comparing the backward masking performances of the schizophrenia-spectrum patients and control subjects

Main effects, interactions	df	F	p
Group	1,47	70.81	< 0.0001
Task	1,47	1.21	> 0.2
ISI	4,188	278.43	< 0.0001
Group by task	1,47	4.09	< 0.05
Group by ISI	4,188	6.46	< 0.001
Task by ISI	4,188	23.04	< 0.0001
Group by task by ISI	4,188	0.76	> 0.5

ISI interstimulus interval

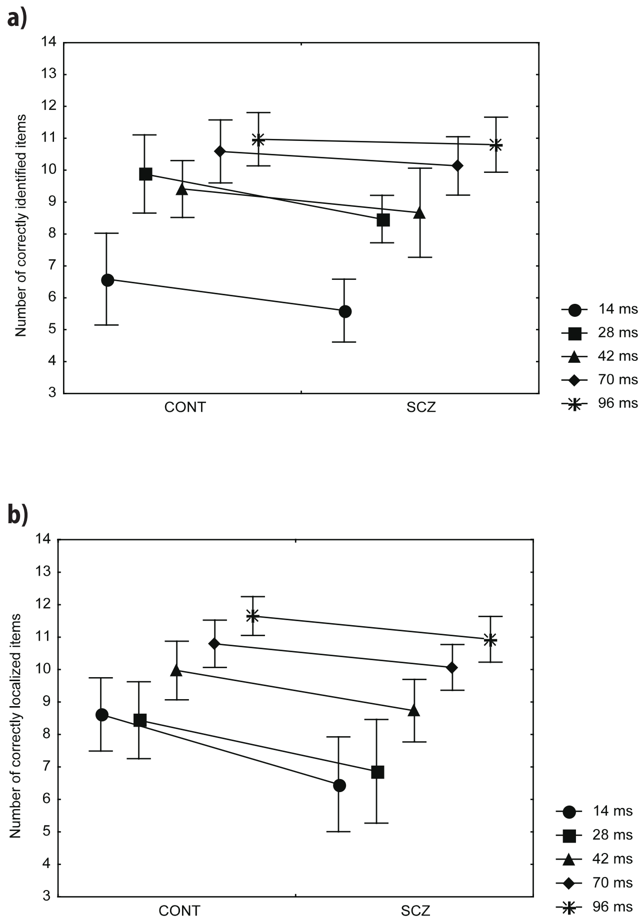

Fig. 1 Visual backward masking performance of the control subjects (CONT) (N=34) and schizophrenia-spectrum patients (SCZ) (N=15) in the target identification (**a**) and target location tasks (**b**). Error bars indicate standard deviations.

1997, 1999). The result of this comparison was significant ($F(1,47)=20.37$, $p < 0.0001$), suggesting that the patients demonstrated more pronounced deficits at short ISIs (Fig. 1).

Finally, we performed planned comparisons with F tests to explore non-linear trends in the masking performances. In the target identification test, the controls exhibited a significant cubic trend (N-shaped masking function) ($F(1,47)=21.74$, $p < 0.0001$), whereas in the patient group only a marginal effect was observed ($F(1,47)=3.79$, $p=0.058$). The between-group analysis was not significant ($p > 0.2$). In the target location test, the controls had a quadratic trend (U-shaped masking function) ($F(1,47)=6.00$, $p < 0.05$), whereas the patients did not show such effects ($p=0.63$). Again, the between-group analysis was not significant ($p > 0.2$) (Fig. 1). All aspects of BM results remained essentially the same when the medicated patients were excluded or when only the individuals with schizophreniform disorder were included.

Discussion

To our knowledge, this is the first study to show that remitted individuals with schizophreniform disorder exhibit BM deficits. These results, in accordance with data from remitted schizophrenia patients (Miller et al. 1979; Green et al. 1999; Kéri et al. 2000), from unaffected biological relatives of schizophrenia patients (Green et al. 1997; Kéri et al., in press), and from subjects with schizotypal signs (Braff 1981; Merritt and Balogh 1989) indicate that the BM dysfunction is a trait marker of schizophrenia-spectrum disorders. Furthermore, longitudinal studies involving the same patient population is necessary to confirm this hypothesis.

It is important to take into consideration that our patients had relatively spared working memory functions, suggesting sufficiently preserved prefrontal functions. In the case of a more prominent prefrontal pathology and negative symptoms, additional decline may appear in the BM performance together with working memory abnormalities (Butler et al. 1996; Voruganti et al. 1997; Wong et al. 1997). It must be noted that although we tried to test all components of working memory (WCST and digit span backward for the central executive, digit span forward for the phonological loop, and spatial delayed response for the visuo-spatial sketchpad), it can not be excluded that some neglected functions were impaired in our patients (Hutton et al. 1998; Diforio et al. 2000).

While our data clearly show the differential characteristics of working memory and visual information processing functions in remitted schizophrenia-spectrum patients, results from other studies reveal a more heterogeneous picture. Although it has been demonstrated that relatives of schizophrenia patients show working memory impairments (Park et al. 1995; Conklin et al. 2000), there is a degree of heterogeneity even within non-remitted schizophrenia patients (Goldberg et al. 1988; Braff et al. 1991; Goldstein et al. 1996; Morice and Delahunty 1996), and normal prefrontal activation has been also reported (Manoach et al. 1999). Concerning the information processing hypothesis, despite the numerous replications of BM deficits (Braff 1993), Rund (1993) found that non-chronic schizophrenia patients performed normally in the BM task. Harvey et al. (1996) reported similar negative results from subjects with schizotypal personality disorder. Bogren and Bogren (1999) measured only a slight BM deficit among outpatients with schizophrenia. Although Green et al. (1997) and Kéri et al. (in press) found affected BM performances in non-psychotic relatives of schizophrenia patients, in a previous report Lieb et al. (1996) reported intact BM functions in adolescents at high risk for schizophrenia. The results of the present study supports the view that the BM dysfunction is a trait-marker of schizophrenia-spectrum disorders, even when various aspects of working memory are preserved.

A powerful theory for multiple domains of visual working memory delineated two parallel systems, the "What" and "Where" pathways (Goldman-Rakic 1999). This theory is particularly useful, because it may build a bridge between basic-level information processing (e. g. BM) and higher-level cognitive functions. Early analysis of visual information is mediated by transient and sustained channels, which are believed to be the analogs of primate retinogeniculate magnocellular and parvocellular pathways, respectively. The transient system is sensitive for low spatial frequencies and rapid spatiotemporal changes, whereas the sustained system is responsible for the analysis of high spatial frequencies, stationary patterns, and hue (Breitmeyer and Ganz 1976; Lennie 1980; Bassi and Lehmkuhle 1990). The two channels may interact in the primary visual cortex (V1). From the V1, the dorsal (occipito-parietal) stream is related to spatial and motion perception, eye-movements, and other visuomotor actions ("Where" pathway). In contrast, analysis of form, color, and faces is housed in the ventral (occipito-temporal) regions ("What" pathway) (Van Essen et al. 1992). The anterior part of the ventral system is closely related to semantic memory and language (Büchel et al. 1998). Although transient and sustained channels have been shown to interact in the cortex, recent research found that the ventral system relies on information from the sustained channels and the dorsal system on the transient channels (Kessels et al. 1999). Finally, the occipito-parietal stream projects to the dorsolateral prefrontal cortex, while the ventrolateral prefrontal cortex receives its major input from the occipito-temporal areas. These prefrontal structures are thought to be responsible for the active maintenance of domain specific visual information (Goldman-Rakic and Selemon 1997; Goldman-Rakic 1999; but see Postle and D'Esposito 1999; Owen et al. 1999).

In some circumstances, the BM phenomenon is associated with an interaction of sustained and transient channels. Integrative BM occurs when the images of the target and mask are fused in the iconic memory. In interruptive BM, the representation of the target is disrupted by the mask, which is initially mediated by the transient channels. In target identification tests with high-energy masking, both integrative and interruptive mechanisms are present. In contrast, in the currently used target location paradigm interruptive mechanisms predominate, together with a transient channel involvement in the processing of the target (Turvey 1973; Breitmeyer and Ganz 1976; Green et al. 1994 a, 1994 b; Cadenhead et al. 1998).

Our results indicate that remitted patients with schizophrenia-spectrum disorders are especially impaired in the target location task, emphasizing the disorder of interruptive masking and transient-transient cortical interactions (Kéri et al. 2000). This is consistent with previous reports from schizophrenia patients (Schwartz et al. 1987; Green et al. 1994 a, 1994 b; Suslov and Arolt 1997; Cadenhead et al. 1998; Kéri et al. 1998; Slaghuis 1998). In addition, this is the first demonstration of target location BM dysfunctions in remitted, highly functioning patients. In the Green et al. study (1999), which was designed to investigate a remitted schizophrenia population, a blurred target (low spatial frequency) condition was included to examine transient channels. In that test, a marked deficit was found, although the group by task interaction was not significant. An additional finding, confirming earlier data from healthy biological relatives and remitted patients, is that the BM deficit is more pronounced at shorter ISIs, which may reflect automatic, sensory-perceptual processes (Green et al. 1997; Kéri et al., in press).

As in other studies, we obtained a cubic (N-shaped) masking function in the target identification task and a quadratic (U-shaped) masking function in the target location task (Cadenhead et al. 1998; Green et al. 1999). However, the individuals with schizophrenia-spectrum disorders had less marked tendencies to achieve N-shaped and U-shaped curves. Green et al. (1999) found similar effects in their remitted patients and they attributed the origin of this quantitatively different masking function to disturbed cortical oscillations. An important contribution to these data comes from the target location condition, where the patients did not display a U-shaped psychometric curve. However, in our study the between-group comparisons were not significant, possibly because of the poorer temporal resolution and smaller sample size.

Examining higher levels of the "What" vs. "Where" model, O'Donnell et al. (1996) found that schizophrenia patients had selective deficits in the discrimination and recognition of spatial information as contrasted with object information. The deficit was more severe when a delay period was inserted between sample and test items, suggesting the vulnerability of spatial working memory. In a carefully conducted series of studies, schizophrenic patients and their unaffected relatives demonstrated a selective deficit in motion perception, which correlated with the disturbances of smooth-pursuit eye movements (for a review, see Holzman 2000). On the other hand, Fleming et al. (1997) reported anomalies in spatial working memory but not in spatial perception, and Farmer et al. (2000) found normal trajectory discrimination of moving dots in patients with schizotypal personality disorder. Strikingly, the same patients showed significant working memory anomalies for the same stimuli. Therefore, data from the Fleming et al. (1997) and Farmer et al. (2000) study suggest that the prefrontal system devoted to the maintenance of spatial and motion information can be impaired when lower-level perceptual processes are spared. In this context, it is of particular interest that we found anomalous transient-transient cortical interactions in patients with spared spatial working memory, suggesting that in the "Where" system downstream abnormalities may be present in the absence of higher-level deficits, especially when rapid temporal changes must be processed.

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